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Cu-Catalyzed Three-Component Carboamination of 2-arylacrylates

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Cu-Catalyzed Three-Component Carboamination of 2-arylacrylates

by

Andrei Popov

Thesis

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Dedication

For my beloved wife and family

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A special place in this Acknowledgment is intended for my family. I would like to thank my parents for supporting me in this quite daredevil decision to travel across the ocean and start a new chapter in my life. And, of course, this would not happen without the principal source of my inspiration, my wife, Nadya. You were the person who planted the seed called “Go to US Grad School, you can do it!” in my brain and pushed me out of my comfort zone to travel into a great unknown and discover the whole universe of opportunities here. I love you 3000.

Abstract

Cu-Catalyzed Three-Component Carboamination of 2-arylacrylates

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Supervisor: Kami L. Hull

There is an increasing demand for modern methods to construct one of the most ubiquitous bonds in biologically active molecules: a carbon-nitrogen bond. Transition metal catalysis represents a powerful tool to create new chemical bonds with great efficiency and selectivity. Thus, the development of novel catalytic techniques, based on transitions metals, for quick and effective assembly of nitrogen-containing organic molecules can be an advancement in synthetic routes to many drug molecules, agrochemicals, functional materials and many others.

1,2-carboamination of alkenes is the approach that unlocks the access to rapid assembly of complex organic nitrogen-containing frameworks from readily available feedstocks. In particular, the carboamination of acrylates can provide a synthetic access to various aminoacid derivatives. The present thesis is devoted to the development of the Cu-catalyzed carboamination of 2-arylacrylates. A wide substrate scope with good functional group tolerance is demonstrated. The mechanistic aspects of the reaction are discussed.

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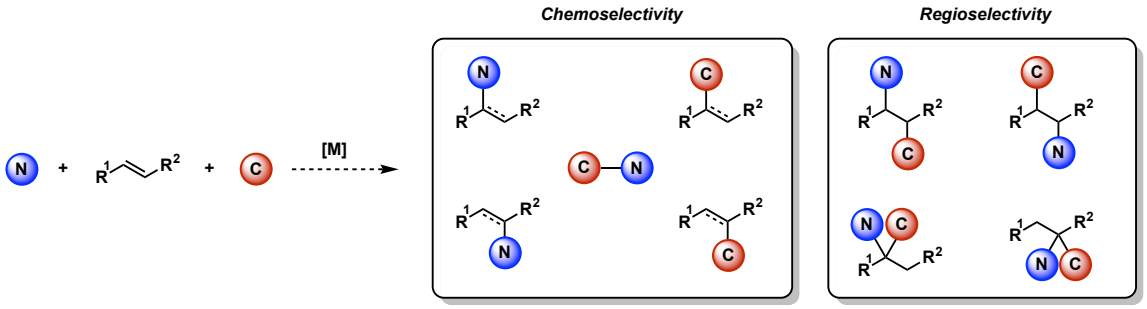
CHAPTER 1. LITERATURE REVIEW

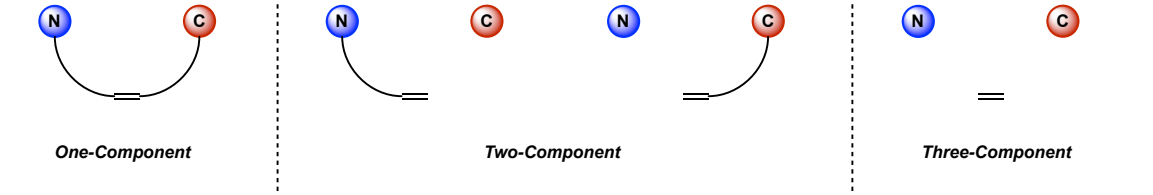
1.1 Introduction and background

84% of the compounds from the "World's Top 200 drug molecules" have at least one carbon-nitrogen bond, with 58% containing a N-heterocycle[1,2]. It can be amino-, amide or some nitrogen-containing heterocyclic fragment. Provided the ubiquity of carbon–nitrogen bond in biologically active compounds, design of novel and efficient tools for their synthesis remains a significant challenge for modern organic chemistry. 1,2-Difunctionalization of olefins represents a powerful and feasible approach for the synthesis of complex nitrogen-containing frameworks from cheap and available feedstocks. In particular, carboamination concept theoretically allows one to install both nitrogen- and carbon-containing moieties in a single step. Given the complexity of coupling three functional groups in a single reaction to assemble a complex structure from different C- and N- sources, a number of side products with undesirable chemoselectivity may be expected. These include cross-coupling between C- and N-moieties, hydrofunctionalization products, or carboamination products with the opposite regioselectivity. In order to overcome these challenges, many approaches to olefin carboamination use substrates where either or both carbon and nitrogen moieties are tethered to the olefin, or just one component (C- or N-) component is linked and reacts with an exogenous reagent. Thus, these approaches can be described as "one-component carboamination" and "two-component carboamination" respectively. Despite the prefabrication prerequisites, this transformation is of a big synthetic importance because it represents a powerful tool to obtain various useful nitrogen-containing annulated products. However, the recent advent of application of radical chemistry[3] and photoredox catalysis[4–

[6] to the 1,2-difuctinalization of alkenes paved a road to the development of genuine, fully modular three-component carboamination reactions.



Scheme 1.1: Challenges in 1,2-carboamination



Scheme 1.2: Various tethering strategies

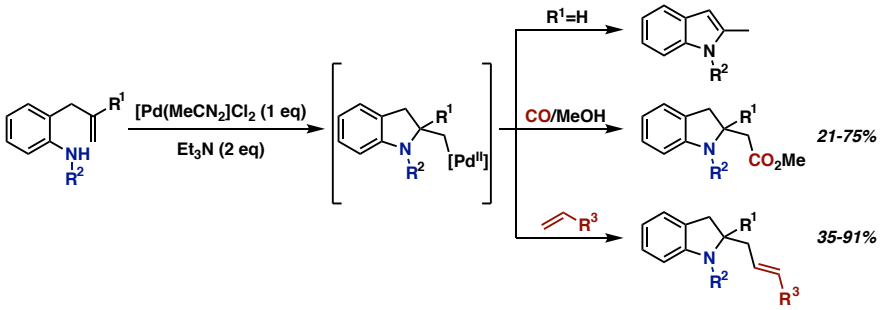
The present review is aimed at encompassing the evolution of the approaches to the carboamination from one-component systems to fully intermolecular three-component.

1.2 Two-Electron Logic in Olefin Carboamination

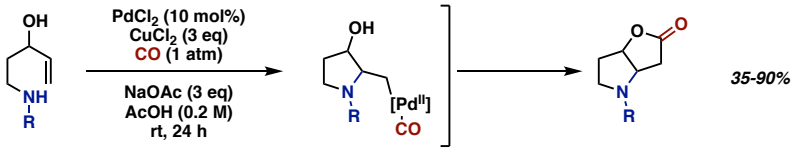
1.2.1 Two-Component Carboamination

One of the very first examples can be tracked back to 1980, when Hegedus and co-workers described a Pd-mediated Wacker-type carboaminative heteroannulation[7] from a substrate bearing both olefin fragment and amino group (Scheme 1.3). The reaction occurs

via *anti*-aminopalladation followed by the capture of the resulting Pd(II) intermediate. To capture the intermediate, the authors made use of an additional olefin or alcohol/CO combination to give a corresponding carbon moiety. Interestingly, this transformation was demonstrated to be sensitive to the R group nature. When R^1 = H and no carbon moiety available to install, a competitive β-hydride elimination takes place to yield an indole derivative. Moreover, a substituent on the amine function is required to avoid the formation of isocyanates via direct carbonylation. These nuances put certain restrictions on the possible substrate scope for this reaction. In 1985, Yoshida and co-workers published a similar approach[8] for the synthesis of fused cyclic hexahydro-*2H*-furo[3,2-*b*]pyrrol-2-one derivatives via aminocarbonylation of 3-hydroxypent-4-enylamides. In this example, the acyl-Pd(II) intermediate undergoes an intramolecular alcoholysis (Scheme 1.4).

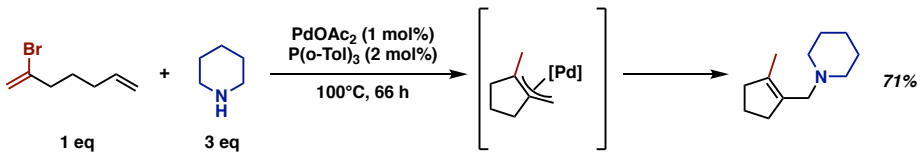


Scheme 1.3: Wacker-type Pd-assisted carboaminative heteroannulation



Scheme 1.4: Wacker-type Pd-catalyzed heterocyclization

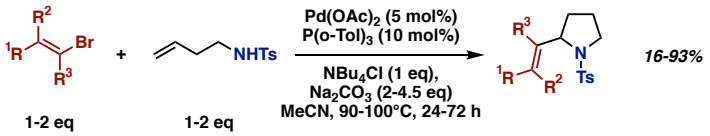
In 1983, Heck and co-workers explored the idea first published in 1978 towards a two-component carboamination[9]. The authors made use of vinyl halides and triflates as a second component in carboamination of olefin tethered to the amine[10]. Unlike the Wacker-type carboamination processes, this reaction occurs though a carbopalladation over the C=C double bond to deliver a π-allyl Pd complex followed by a C-N bond formation (Scheme 1.5). The formation of stable π-allyl-Pd(II) intermediates avoid the undesirable side reactivity connected with b-hydride elimination. On the other hand, a competitive Mizoroki-Heck reaction still may take place in these systems. Thus, the nature of the nucleophile and its affinity towards the key π-allyl-Pd(II) intermediate play a significant role in the chemoselectivity of the reaction. This aspect falls in line with the observation made by Balme and Gore[11] that in similar conditions basic amines never interacted with alkyl Pd(II) species to yield a carboamination product. Only Mizoroki-Heck coupling takes place. Whereas carbanionic species generated from malonate did deliver a corresponding product.



Scheme 1.5: Two-component carboamination via external amine

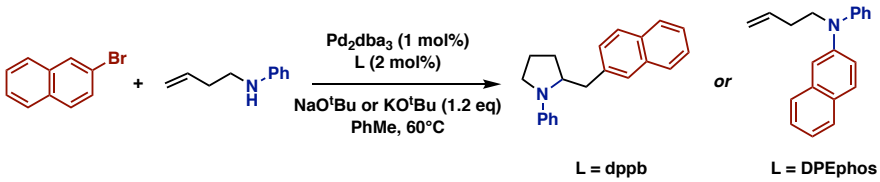
In 1994, Weinreb and Larock described a similar approach to two-component carboamination reaction[12]. The reaction occurs through oxidative addition of C-X bond to Pd^0 followed by carbopalladation of the olefin, formation of a π-allyl Pd intermediate and a cyclization via nucleophilic attack of the amine onto allylic species (Scheme 1.6). The reaction can yield various vinyl derivatives of N-heterocycles such as pyrrolidines and

piperidines. Interestingly, this work confirmed the observation made by Balme and Gore[11]. When the amine moiety did not have an electron withdrawing substituent, only Heck product was received. When tosylated and triflated derivatives were used, the cyclization occurred to deliver the desirable products with the moderate to high yields.

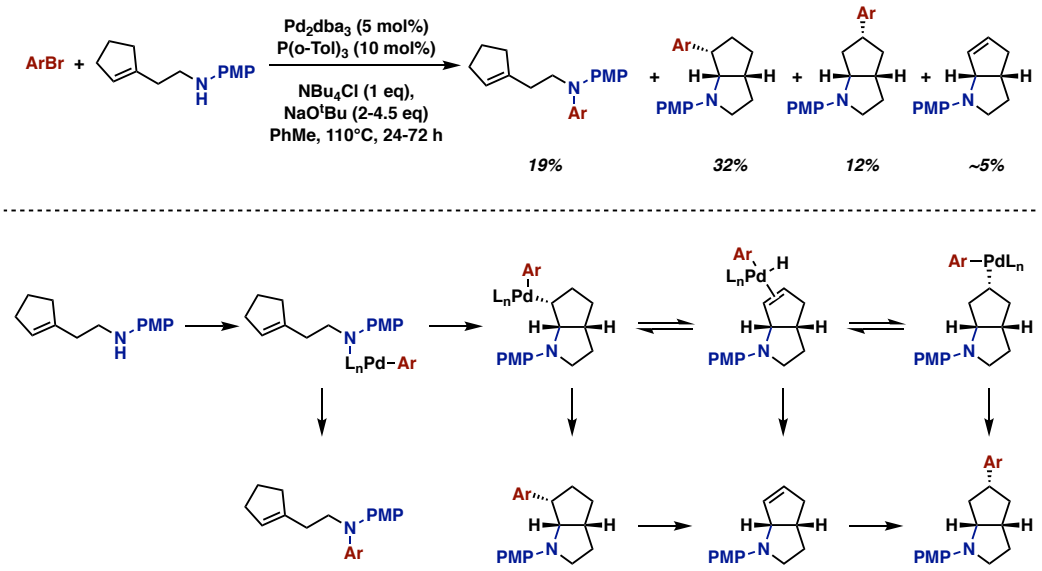


Scheme 1.6: Two-component carboamination reported by Weinreb and Larock

A big advance in Pd-catalyzed carboaminative annulations is related to the works published by Wolfe and co-workers. His group reported a series of carboamination cyclization reactions[13], where nucleophilic N-component is also bound with olefin. To capture Pd intermediates in their initial studies, the authors used various aryl bromides[14]. Noteworthy, the authors claimed they described the first example of an intramolecular olefin insertion into a [ArPd(II)(NRR')] intermediate to form a C-N bond[15]. This step is relatively sensitive to the ligand nature. For example, when Pd_2dba_3/DPEphos catalytic system was used on the initial system (Scheme 1.7), an N-arylation product was a predominant one. However, bidentate phosphines, such as dppe and dppb, could lead to a desirable pdt due to their ability to slow down the reductive elimination from the [ArPd(II)(NRR')] intermediate to give a Buchwald-Hartwig N-arylation product. When using the substrates with terminal alkenes, the regioselectivity values ranged from 10:1 up to 100:1 in some cases. In case of internal alkenes, the reaction yielded in a mixture of several products. Nevertheless, this experiment was crucial for the mechanistic studies on this reaction.



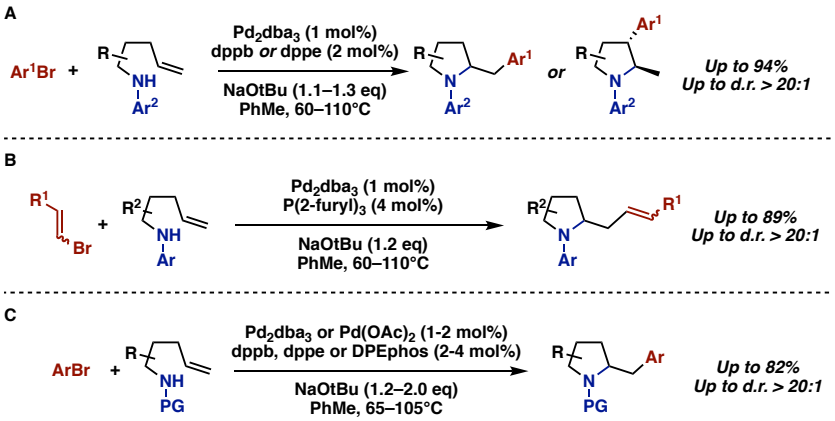
Scheme 1.7: Wolfe-type two-component carboamination



Scheme 1.8: Mechanistic investigations of Wolfe carboamination

The reaction mechanism implies a typical for Buchwald-Hartwig amination sequence of an oxidative addition of ArBr to Pd(0) followed by base-assisted amination of (Ar)Pd(II) intermediate to give [ArPd(II)(NRR')] species. Then an annulation through 1,2-migratory insertion of N-group takes place. Lastly, a reductive elimination to yield a product and transform Pd(II) to Pd(0), closing the catalytic cycle. An insertion into Pd-C bond for [ArPd(II)(NRR')] species would lead to an intermediate, where the Ar substituent is attached directly onto the ring. However, these species are not expected to yield the products with migrated aryl group, which, however, were observed under the reaction

conditions. Another argument stated that, under reaction conditions, the intermediate formed after insertion into Pd-C bond would undergo a β-hydride elimination to yield a Schiff base which was not detected. Instead of that, [ArPd(II)(NRR')] undergoes an insertion into Pd-N bond. If the substrate used assumes the formation of chiral centers in course of the reaction, the aminopalladation step occurs as a *syn*-addition. And the subsequent reductive elimination occurs with retention of the configuration.



Scheme 1.9: Carboamination of various substrates reported by Wolfe and co-workers

Later on, the carbon moiety scope was expanded more toward vinyl[16,17] bromides (Scheme 1.9B). The side reaction of *N*-vinylation was the most challenging aspect when using alkenyl bromides. This drawback was substantially mitigated when P(2-furyl)$_3$ was used instead of bidentate dppe or dppb. This catalytic system significantly slows the reductive elimination to yield a side product.

The approach developed is of a great interest for the rapid assemble of different substituted *N*-arylpyrrolidines. However, the further synthetic operations with the derivatives scope are complicated due to the necessity to remove a *p*-methoxyphenyl protecting group. Moreover, the presence of an electron rich aryl fragment increased the

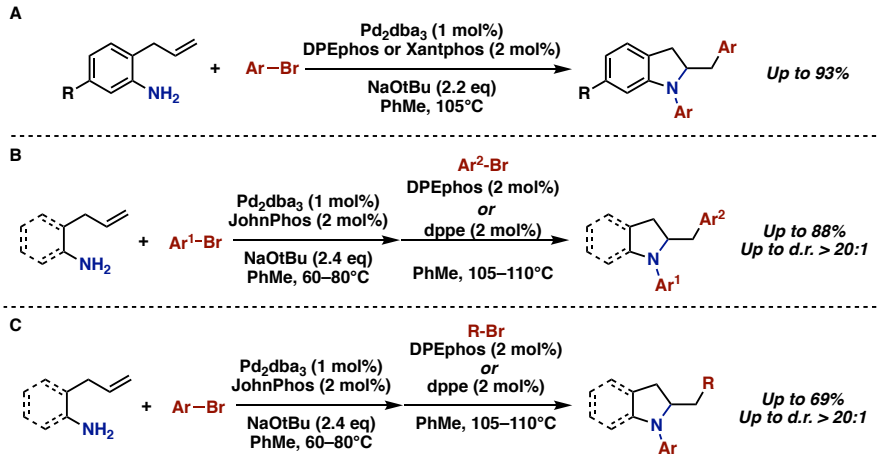
yields of the isomeric 3-arylpyrrolidines (up to 10% in some cases) and increased contribution of *N*-arylation side products. In order to avoid the undesirable selectivity and expand the substrate scope toward a broader range of *N*-substituted γ-aminoalkenes the authors made use of various N-protected amine derivatives, bearing acetyl (Ac) and *tert*-butyloxycarbonyl (Boc) protecting groups (Scheme 1.9C)[17,18]. The authors found that these substrates can be efficiently converted into *N*-protected pyrrolidine derivatives with good yields and diastereoselectivities similar to those observed for *N*-PMP-substrates. Noteworthy, the formation of 3-arylpyrrolidine side products was not observed. Moreover, the transformations were found to be efficient even with electron-poor aryl bromides and alkenyl bromides.

N-arylamines that were used as the substrates for carboamination can also be prepared through Pd-catalyzed C-N cross-coupling. Since both cross-coupling and carboamination are catalyzed by palladium, Wolfe and co-workers explored the possibility to transform this process into a two-step tandem reaction where *N*-arylation is followed by carboaminative cyclization. To study the viability of this approach, 2-allylaniline and its derivatives were used as starting materials and found to give *N*-aryl-2-benzylindolines with moderate to very high yields (Scheme 1.10A). Electron rich aryl bromides, such as 4-bromoanisole, required some minor adjustments of the catalytic system, such as introducing Xantphos ligand to avoid Heck coupling with terminal double bond.

Having demonstrated the ability to start the transformation directly from primary amines, Wolfe and his team aimed at making the approach even more modular by utilizing two different aryl bromides (Scheme 1.10B). The goal was to perform a two-step process, where amino group is being arylated with one aryl bromide at the first step followed by the injection of the second aryl bromide that serves as a carbon moiety for the carboamination step. To selectively form *N*-arylation product and prevent further *N*-arylation over

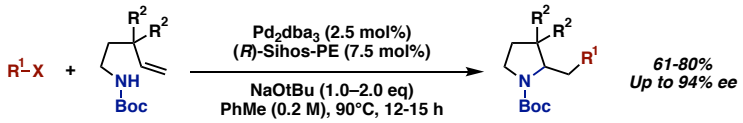
cyclization, the authors proposed to change the electronic properties of the palladium catalyst by introducing a bidentate DPEphos ligand to form a new complex *in situ* rather than isolate the product and subject it to another reaction.

Overall, a developed two-step one-pot process involved the reaction of 2-allylaniline with bromobenzene in the presence of Pd_2dba_3/JohnPhos catalytic system and a base. Upon a full consumption of the bromobenzene, a catalytic amount of DPEphos was injected followed by the addition of 2-bromonaphthalene. In case of aliphatic γ-aminoalkenes dppe was used instead of DPEphos to produce N-arylated pyrrolidines. Having reached the success with the application of the two-step approach, the authors extrapolated it onto the synthesis of 2-allyl pyrrolidines and indolines using vinyl bromides as a second coupling partner (Scheme 1.10C). The same protocol involving Pd_2dba_3/JohnPhos on the first step followed by DPEphos or dppe on the second step was found to be effective giving the resulting cyclic products with good yields.



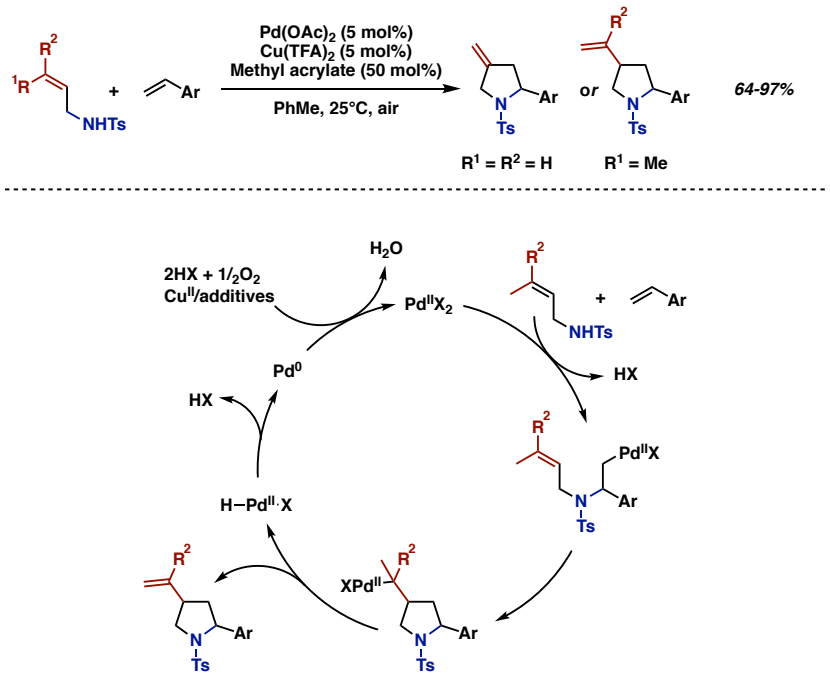
Scheme 1.10: Tandem carboamination reactions developed by Wolfe and co-workers

In 2010, Wolfe and co-workers described the asymmetric version of the reaction[19]. The authors demonstrated the ability of chiral phosphine ligands to yield the carboamination products with the yields up to 80% and *e.e.* values up to 94%.



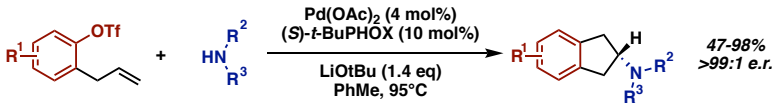
Scheme 1.11: An asymmetric variation of Wolfe-type carboamination

To sum up, the papers highlighted above describe a subset of two-component carboamination reactions where a bifunctional agent, containing a nitrogen fragment tethered to an alkene, is coupled with a carbon moiety. Stahl and co-workers described another variation of two-component carboamination of alkenes with allylsulfonamides[20]. In this example nucleophilic amino group is bound with an alkene that acts as a carbon moiety. Another alkene serves as a counterpart in the assemble of the heterocycle. As shown on Scheme 1.12, the reaction mechanism starts with the aminopalladation of the external alkene followed by the insertion of the allyl double bond into Pd-C bond to close the cycle. Finally, β-hydride elimination occurs to yield the pyrrolidine product. The reaction exhibits a significant improvement in yields when a Cu(II) cocatalyst and additives, such as methyl acrylate, applied. The authors proposed these additives to contribute a positive impact on the stability of Pd(0) intermediates and avoid palladium black formation.



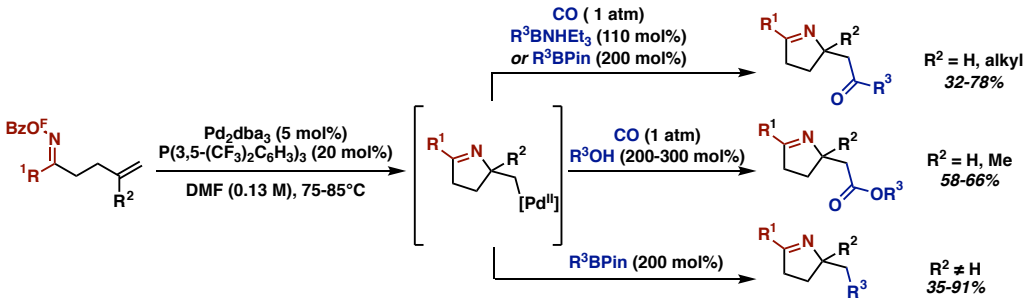
Scheme 1.12: Pd-catalyzed two-component carboamination reported by Stahl and co-workers

In 2015, Wolfe and his group demonstrated the ability of intermolecular amine delivery in the carboamination of the electrophile-tethered olefins[21]. The authors reported the reaction can be performed in enantioselective mode by using a chiral PHOX ligand with yields up to 98% and *e.r.* values up to >99:1. Noteworthy, the reaction goes through a sequential *anti*-aminopalladation/C-C bond forming reductive elimination. The nature of the aminopalladation step was explored via isotope labeling.



Scheme 1.13: Asymmetric two-component carboaminaton via external amine delivery

In 2015, Bower and co-workers reported an umpolung approach to two-component carboamination[22]. In their system, a Pd catalyst activates the N-O bond of O-pentafluorobenzoyl oxime esters followed by the aminopalladation of the tethered olefin to deliver a key alkyl-Pd(II) intermediate. These species trap a nucleophilic carbon moiety and form the product via C-C forming reductive elimination. Carbonylative variant of this transformation is also reported. The reaction is basically a logical extension of 5-*exo*-trig cyclization of iminyl radical linked to an olefin but made in $2e^-$ logic via Pd catalysis. The chemistry using these substrates was further explored by other groups towards photoredox catalysis.

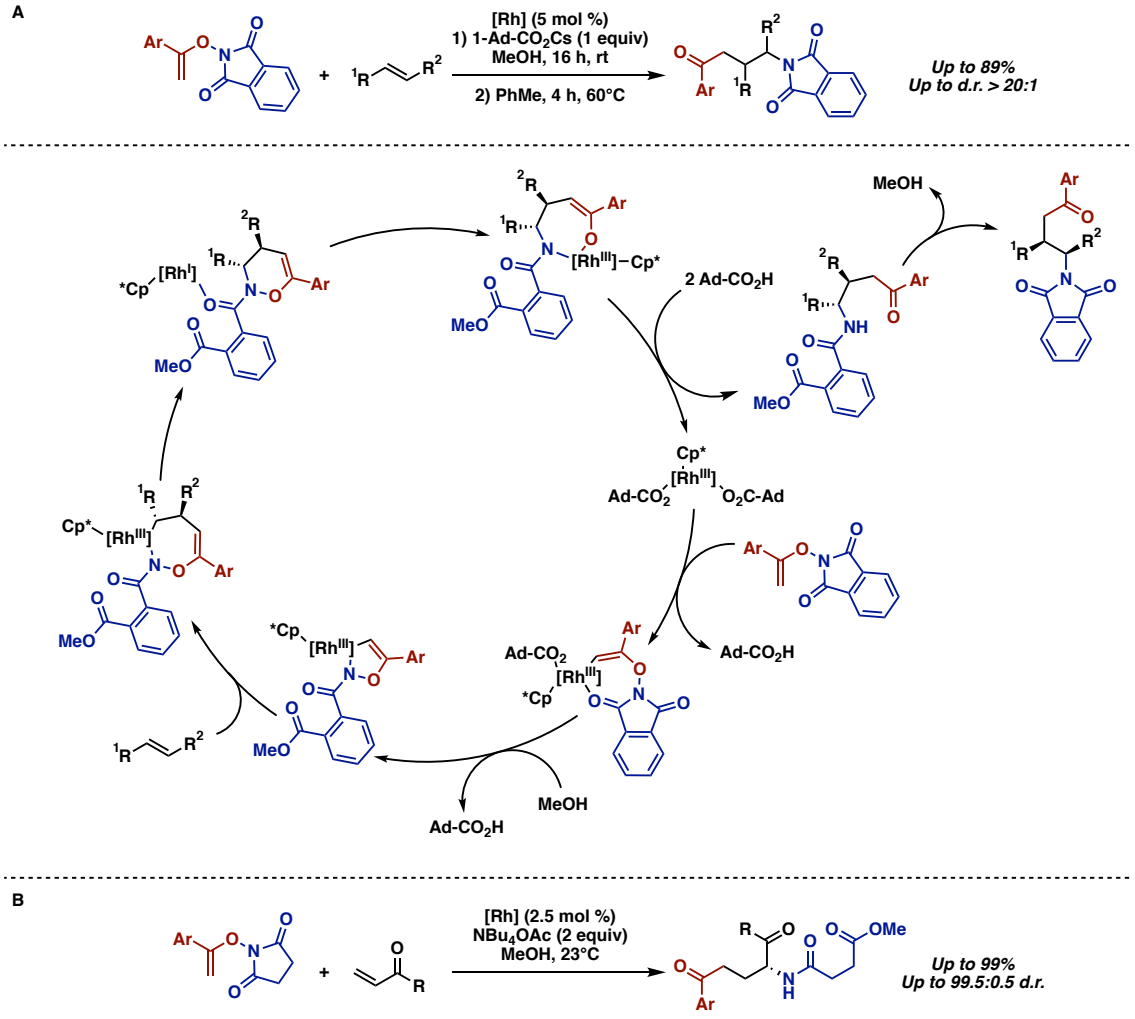


Scheme 1.14: Umpolung two-component carboamination with electrophilic amine source

Rovis group reported[23] a unique mode for two-component Rh-catalyzed carboamination strategy where both carbon and amine moieties come from enoxyphthalimides. Using such reagent, the authors could address the challenge of making acyclic carboamination products. All previously reported two-component carboamination methodologies could lead only to cyclic molecules due to the fundamental limitation of having two reactive functionalities connected with a linker (Scheme 1.15A).

The reaction occurs through a C(sp^2)-H bond activation, with methanolized phthalimide moiety acting as a directing group. After the metallocycle expansion via olefin

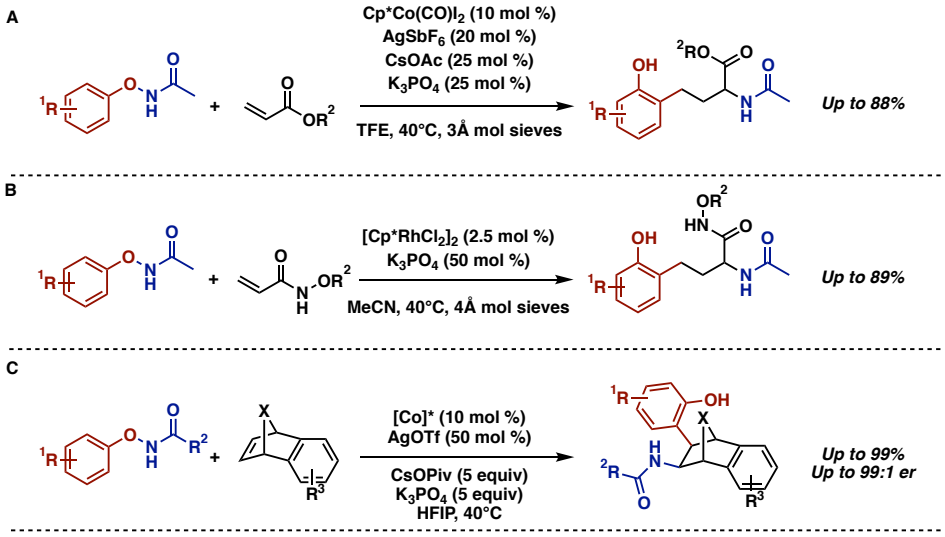
syn-insertion, a C-N bond forming reductive elimination takes place, and cyclic intermediate is ejected. After that the intermediate undergoes a subsequent N-O bond activation followed by organometallic species protonolysis and phthalimide restoration to deliver a desirable carboamination product. Noteworthy, in the absence of nucleophilic alcohol the reaction fails to deliver the desirable chemoselectivity and yields a competitive cyclopropanation product. Although the transformation unlocks the access to acyclic products inaccessible by using amine-olefin- or carbon-olefin-tethered moieties, technically, it is still a two-component carboamination. The necessity of pre-making the bifunctional enoxyphthalimides impose certain restrictions on reaction modularity. Later, the approach with a transient phthalimide directing group was explored deeper by Cramer[24]. The authors applied chiral Rh(III) complexes to achieve a highly chemoselective and enantioselective carboamination of various terminal acrylates and acrylamides to access a vast scope of unnatural α-aminoacid derivatives with *e.r.* values up to 99.5:0.5 (Scheme 1.15B).



Scheme 1.15: Rh-catalyzed two-component carboamination with enoxyphthalimides

The initial report[23] by Rovis was followed by Liu[25] and Glorius[26] to describe a similar two-component carboamination mode, with *N*-aryloxyamides being used as N- and C-moieties source correspondently. This approach allowed to broaden the scope of carbon moieties towards arenes. To achieve the carboamination of acrylates and deliver unnatural α-aminoacid derivatives, Glorius and his group used a Cp*Co(III) complex since its Rh(III) analogs could not yield the desirable products due to high side reactivity to produce Heck products (Scheme 1.16A). On the other hand, Liu's development leveraged their

Cp*Rh(III) chemistry of Heck reaction through the directed C-H activation, with *N*-alkoxyacrylamides being used as substrates (Scheme 1.16B). This modification allowed them to modulate the coordinating properties of this functionality, saturate the Rh(III) center of the intermediate and avoid β-hydride elimination. Cramer used Glorius approach is his studies to develop an enantioselective variation of the reaction[27]. The authors presented the system based on a chiral Co complex to perform *syn*-carboamination of internal olefins with the yields up to 99% and *e.r.* values up to 99:1 (Scheme 1.16C). Interestingly, unlike Cramer's previous report[24], chiral Rh(III) complexes were found to be poorly applicable for these substrates.

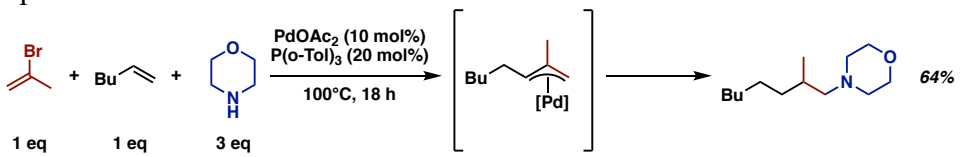


Scheme 1.16: Two-component carboamination with *N*-aryloxyamides

1.2.2 THREE-COMPONENT 2E⁻ CARBOAMINATION

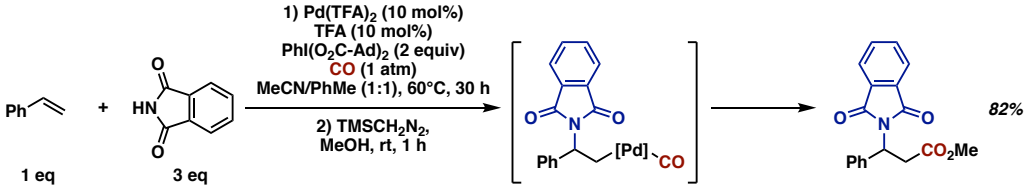
The very first example of fully intermolecular carboaminaton can be tracked back to 1978[9], when Heck was expanding the application of recently discovered Mizoroki-Heck coupling towards the synthesis of allyl amines. The reaction occurs through the sequence

of β-hydride eliminations and migratory insertions to stop at the formation of π-allyl-Pd intermediate followed by an outer-sphere amine attack. Thus, the approach represents the first example of three-component carboamination. The viability of this approach was explored later by Heck[10], Weinreb and Larock[12] towards the synthesis of heterocycles via two-component carboamination.



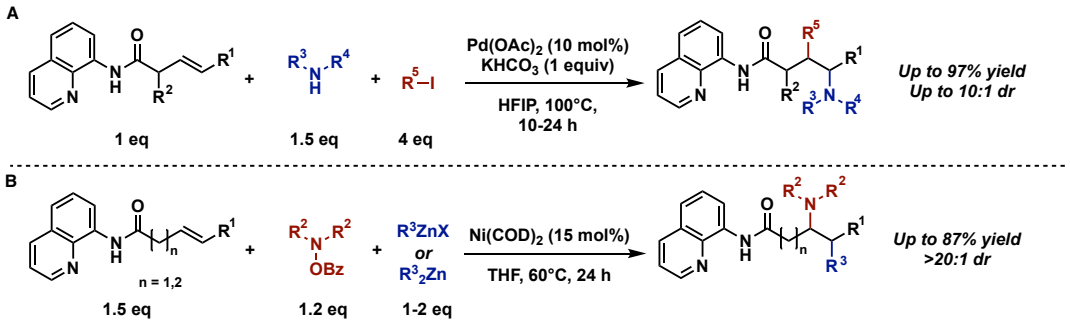
Scheme 1.17: The very first report on three-component carboamination

The other approach based on Wacker-type chemistry, as mentioned above, was developed predominately towards two-component aminocarbonylation. It was not until 2015, when the Liu group reported a three-component Wacker-type carboamination[28]. To enhance the chemoselectivity of the aminopalladation step and avoid an undesirable reduction Pd(II) to Pd(0) by CO, the authors made use of hypervalent iodine reagents, such as $PhI(OAc)_2$ and its analogs. Noteworthy, the role of I(III) reagents was proposed to go beyond just simple oxidants. The kinetic studies demonstrated a higher performance of hypervalent iodine reagents over conventional oxidants, such as 1,4-benzoquinone, and allowed the authors to propose the I(III) compounds may act as Lewis acids to promote the displacement of anionic ligand from Pd(II) species by alkenes and facilitate the aminopalladation.



Scheme 1.18: Wacker-type Pd-catalyzed three-component carboamination

Engle and coworkers reported a three component Pd-catalyzed carboamination reaction of unsaturated amides with amines[29]. This reaction leverages the 8-aminoquinoline auxiliary to act as a directing group and overcome the possible difficulties with chemoselectivity (Scheme 1.19A). Catalytic cycle is proposed to involve Pd(II)/Pd(IV) oxidation states. Thus, carbon moiety scope is limited to alkenyl, aryl and heteroaryl iodides that can easily undergo the oxidation addition to Pd(II). Later, Engle and coworkers published a nickel catalyzed umpolung variation of carboamination reaction that can give the access to the products with the opposite regioselectivity[30]. Given the reversed polarity, N-moiety can be introduced by electrophilic O-benzoyl hydroxylamines, C-moiety – by aryl- and alkylzinc nucleophiles. Despite the necessity to operate aminoquinoline directing groups, these reactions represent an important milestone in the development of fully intermolecular three-component 1,2-carboamination (Scheme 1.19B).

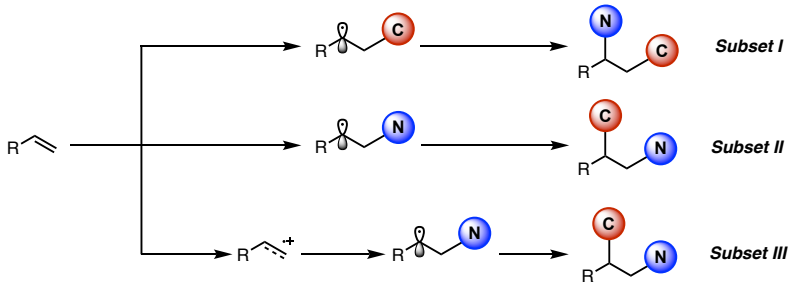


Scheme 1.19: Aminoquinoline directing group strategy for three-component carboamination

1.3 One-Electron Logic in Olefin Carboamination

Despite the considerable progress in the development of olefin carboamination reactions, critical gaps still remain to pursue. A true three-component method would unlock direct access to complex nitrogen-containing compounds with maximum modularity. However, chemoselectivity issue is still a challenge. For example, a side reaction between nucleophilic and electrophilic fragment may lead to undesirable cross-couplings. Hence, to not let N- and C-moiety sources to bybass the actual difunctionalization sequence, certain criteria for facile involvement of alkene moiety are imposed. In order to address these problems, the researchers tend to use various tethering strategies, directing groups or heavily modify the catalytic systems to facilitate the involvement of olefin.

One-electron logic that involves the formation of radicals followed by radical relay is an alternative way to generate active intermediates in olefin carboamination. The addition of the radical into a C=C bond is a fast and efficient process that yields a radical adduct which, in turn, can be involved in the second reaction to install the second fragment on an adjacent carbon and to deliver a vicinal difunctionalization product. Based on the nature of the initially attacking species, olefin radical carboamination reactions can be classified into three different subsets[31].



Scheme 1.20: Three different reaction modes for radical carboamination of alkenes

Subset I involves an initial formation of the C–C bond through addition of a C-centered radical to an olefin followed by C-amination. (Scheme 1.20, Top). In this subset mostly styrene derivatives and various heteroaryl alkenes are used as acceptors for the C-radical and the resulting benzylic radical adduct can be easily oxidized to benzylic carbocation. In this case C–N bond formation is achieved via nucleophilic trapping of the benzylic carbocation. C–N bond formation can also be mediated with a transition metal catalyst or C-radical adducts can directly be trapped by a radical amination reagent. C–N bond formation is generally achieved with cheap and commercially available feedstocks with nucleophilic nitrogen such as amines, amides, azides, nitriles. C–radical precursors are also readily available.

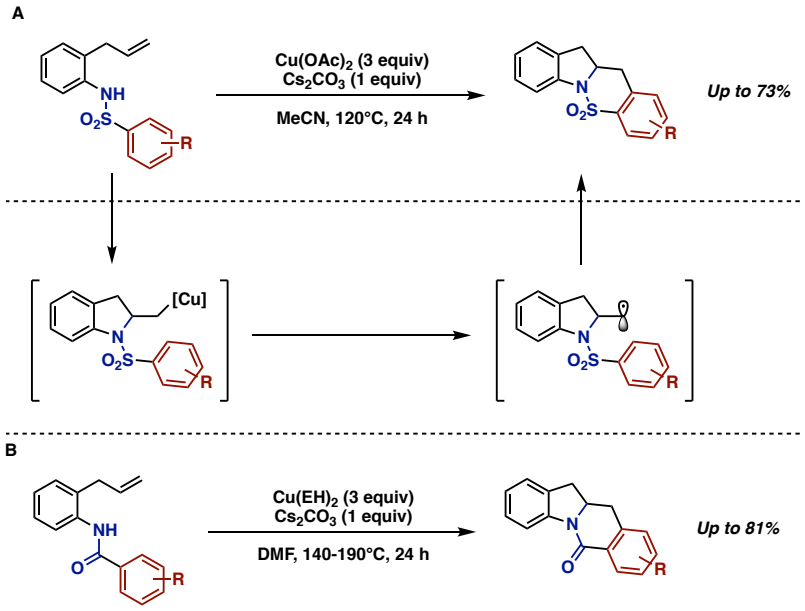
Subset II assumes an initial formation of an N-centered radical followed by a radical relay and C-centered radical trapping (Scheme 1.20, Mid). This approach leads to the opposite regioselectivity; thus, it is often referred to as 2,1–carboamination. In this subset, where is olefin a C-radical acceptor, the difference in reactivity between different substrates has to be controlled by polar effects. Given the electrophilic nature of N-centered radicals species, C–N bond formation is highly chemoselective with an electron-rich alkene, such as an aliphatic alkene, a vinyl ether or an enamide, to give the corresponding nucleophilic C-radical adduct. The adduct can be involved in metal mediated C–C bond formation or trapped either via reaction with a π-acceptor or via sequence oxidation/nucleophilic trapping. Considering the drawbacks, it is worth mentioning that amines or amides often cannot be used as the N-radical precursors without further modifications. In general, this approach requires use of N-heteroatom compounds that are commercially unavailable and must be prepared ahead. Furthermore, sulfonamidyl radicals are mostly reported to have been applied to the carboamination. The sulfonyl group offers high reactivity to the N-radical but on the contrary this functionality is known to not be an

ideal N-protecting group in organic synthesis. Thus, the processes related to deprotection to give a desirable amine are necessary and it may decrease the total yield.

Subset III involves single-electron-transfer (SET) oxidation of the olefin to generate radical cation species that gets trapped with an N-nucleophile to yield a C-centered radical that can be trapped to form C-C bond (Scheme 1.20, Bottom). In the third subset, an alkene substrate undergoes a SET oxidation by a photoredox catalyst to give an alkene radical cation intermediate followed by a nucleophilic trapping with an amine to yield the corresponding C-radical. Finally, C–C bond formation occurs via a radical cyclization to a π-acceptor. There are some limitations regarding the substrate scope, such as only electron rich activated alkenes can be applied. That being said, this subset remains underdeveloped and will not be discussed further.

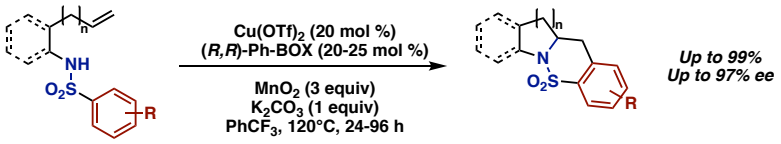
1.3.1 One-Component Carboamination

The most important advance in radical carboamination was made by the Chemler group[32]. Beginning 2007, the team published a series of works on one- and two-component radical carboamination in the presence of copper. The original reports[33–35] being rather a copper-mediated than a catalytic reaction, the authors disclosed an attractive strategy to assemble complex heterocyclic motifs through a radical relay (Scheme 1.21A-B). The reaction occurs via aminocupration of the olefin moiety, which resembles the Pd chemistry earlier reported by Wolfe[13]. However, then the reaction directs through a radical/polar crossover path. The homolysis of Cu-C bond results in the generation of C-radical followed by the radical aromatic substitution into the arene moiety. To afford a rearomatization, another equivalent of copper oxidant is necessary.



Scheme 1.21: Cu-mediated one-component carboamination developed by Chemler and co-workers

A subsequent work[36] reported a transition from bulk copper reagent to a catalytic system (Scheme 1.22). In order to achieve Cu turnover, stoichiometric amounts of MnO_2 oxidant were applied. As a logical extension, the approach was expanded towards enantioselective cycization[36–38]. Using chiral ligands of BOX family allowed the authors to achieve high *e.e.* Furthermore, the asymmetric induction observed in the presence of chiral Cu complex allowed the authors to propose that Cu is directly involved in the C=C bond functionalization, with the radical trapping studies serving as a proof for radical intermediates. Thus, the authors stated the reaction occurs through a *syn*-aminocupration of the alkene moiety to introduce a chiral carbon followed by a radical generation and C-C_{Ar} bond formation to deliver fused polycyclic products[39,40]. The approach was successfully applied to the synthesis of a variety of N-heterocycles, such as piperidines[32], lactams[34], pyrrolidines[36], hexahydro-1H-benz[f]indoles[38] and azabicyclooctanes[41].



Scheme 1.22: Cu-catalyzed net oxidative one-component radical carboamination

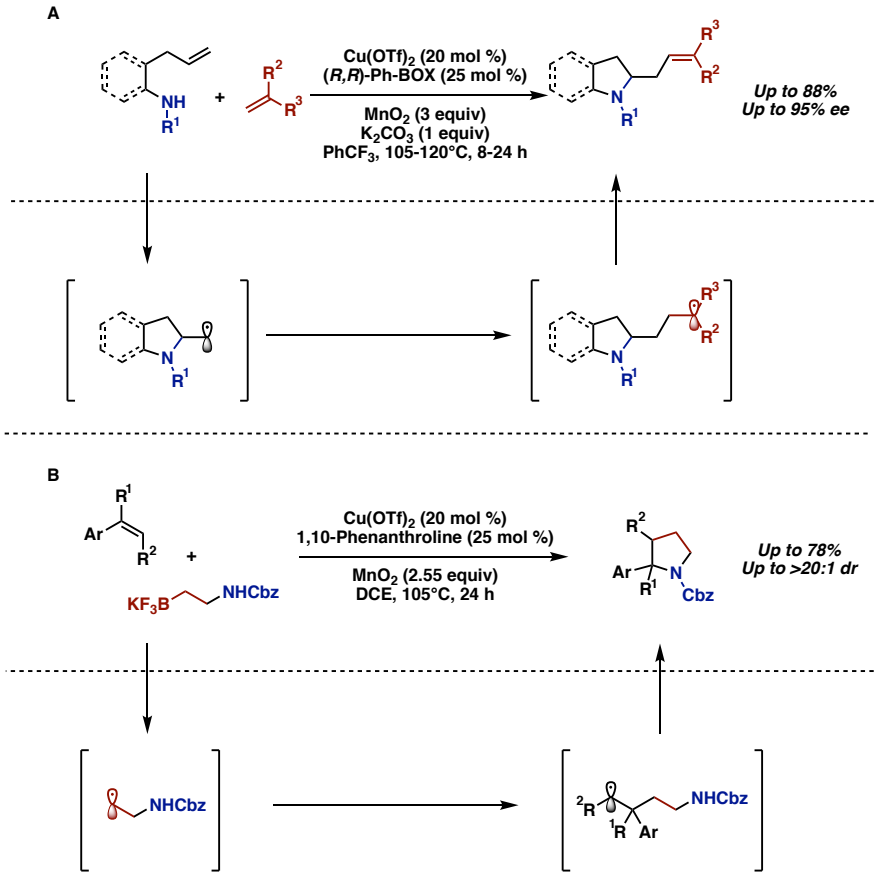
Although it was mostly tethering strategy and careful substrate design that helped to overcome chemoselectivity and regioselectivity issues for one-component reactions, the pioneering works by the Chemler group exhibited a powerful application of copper systems and their ability to operate the reactivity patterns different from the ones reported earlier.

1.3.2 Two-Component Carboamination

Having developed protocols for one-component radical cyclizations, Chemler and co-workers expanded their methodology towards two-component processes[42,43]. The approach shows resemblance to the reactivity mode used in one-component reaction. The key difference lies in using externals alkenes for a radical Heck-type introduction of carbon moiety (Scheme 1.23A). The reaction starts with *syn*-aminocupration of amine moiety tethered to the olefin. Upon the homolysis of the C-Metal bond, the radical intermediate is trapped by an external alkene, with more stable radical being formed. A subsequent oxidation and deprotonation afford the product. Analogously to the one-component system, chiral ligands are capable of performing the reaction in an enantioselective way.

An alternative strategy reported by the Chemler group assumes an entirely different reactivity mode (Scheme 1.23B). In 2016, the authors described a carboamination reaction[44] where carbon and amine moieties are linked, and the radical generation is performed by $1e^-$ oxidation of organotrifluoroborate salt. After the radical addition across the C=C bond, the amination step can be accomplished either via Cu-mediated amination or via further $1e^-$ oxidation/nucleophilic trapping sequence. The authors demonstrated the

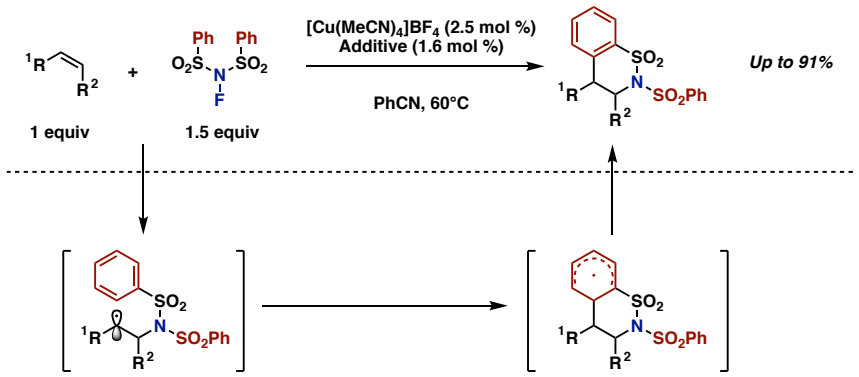
presence of radical intermediates via radical clock experiments. However, they could not distinguish between the different C-N bond formation pathways.



Scheme 1.23: Two-component radical carboamination strategies reported by Chemler and co-workers

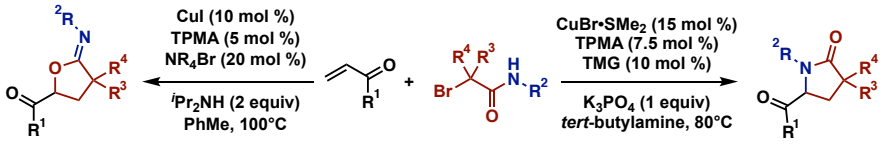
An interesting approach was reported in 2013 by Kanai and co-workers. The authors chose *N*-fluorosulfonimides (NSFI) to serve as both N-centered radical source and C-moiety donor. The generation of N-centered radical occurs through the activation of the electrophilic amine by Cu complex followed by the radical addition and radical aromatic substitution. Unlike Chemler approach, this reaction is a net redox neutral process because the catalytic cycle starts with the oxidation of Cu catalyst. Therefore, the rearomatization

can be achieved via interaction with the oxidized form of the catalyst. No bulk oxidants needed.



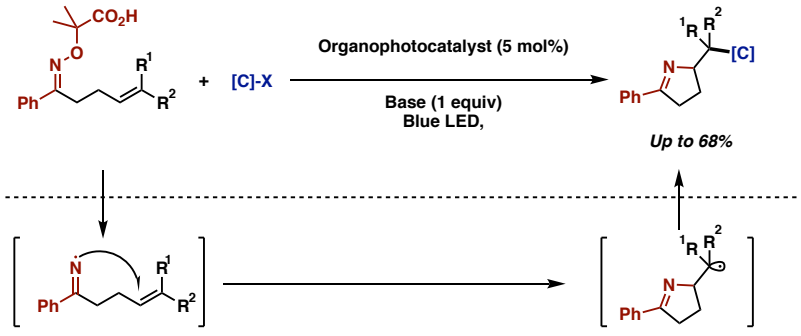
Scheme 1.24: Two-component carboamination with electrophilic amines

Nishikata and co-workers explored the carboamidation of electron-deficient olefins with bifunctional α-bromoamides[45]. The reaction starts with the generation of C-radical through the reduction of α-bromoamide. Then, depending on the conditions, the reaction can go through N- or O-cyclization to yield lactam or iminolactone correspondently. The authors concluded the direction of the cyclization depends on the basicity of the system. To promote a C-N bond formation, strongly basic conditions and amine solvents are required to create a Cu-amide complex[46], which, in turn, undergoes a radical trapping, due to the proximity of the a-carbon-centered radical to deliver a lactam product.



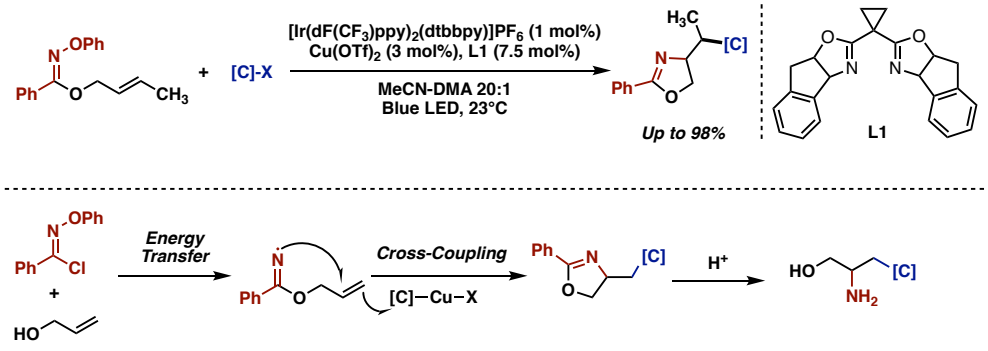
Scheme 1.25: Two-component carboamination of electron deficient alkenes with α-bromoamides

During the last decade, photoredox catalysis became an attractive and efficient strategy for the generation of radical species from various feedstocks, especially to receive N-centered radicals. A number of strategies leverage the structural features of the starting material to avoid undesirable side reactivity and to increase the efficiency of the carboamination process. For example, the N- or C-centered radical precursor can be tethered to the olefin moiety to promote a fast 5- or 6-membered ring formation followed by an introduction of the other coupling partner. In 2017, the Leonori group reproted a flexible process where the iminyl radical 5-*exo*-trig cyclzation is accompanied by a trapping with various SOMOphiles. The cyclizations of the iminyl radicals tethered to the olefins has been exceptionally studied[47]. However, the key difference from the Bower work lies in the nature of SOMOphile used to trap the cyclization products. Since the generation of the iminyl radical occurs via an oxidative fragmentation of the oximes, reductive quenching is required, which makes electrophilic carbon sources suitable for the reaction. Among the examples reported, Leonori and co-workers presented a number of carboamination products that can be obtained via trapping with Michael acceptors, alkenyl and alkynyl halides.



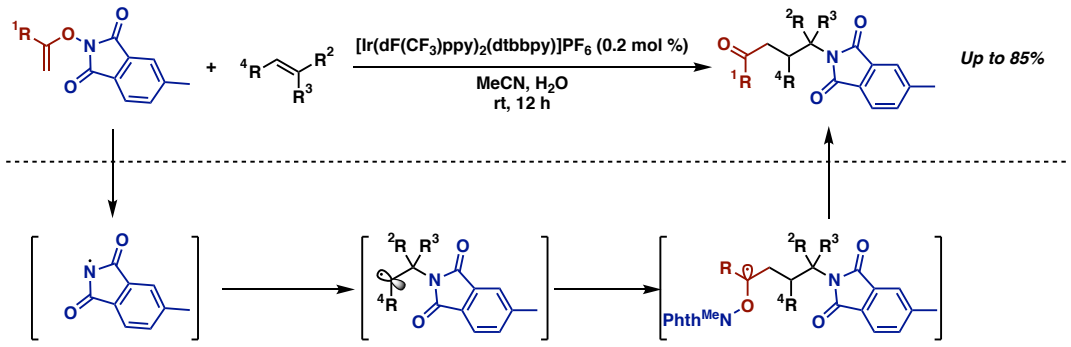
Scheme 1.26: Photoredox two-component carboamination reported by Leonori and co-coworkers

Nagib and his group leveraged the same logic with connecting the N(sp^2)-radical precursor and olefin moiety. However, the choice of the substrates was quite interesting. The authors envisioned the modification of allyl alcohols with N-aryloxyimidoyl chlorides to produce redox-active imidate esters. Under photoredox conditions, these esters can undergo a N-O bond homolysis giving an imidate radical that can rapidly cyclize to produce a C-centered radical. Among possible SOMOphiles to trap the radicals, various π-acceptors proposed, such as Michael acceptors and aryl cyanides[48]. Later, the Nagib group reported a dual catalysis process that merges both photocatalysis and Cu catalysis[49]. Noteworthy, the photochemical portion was carefully designed to not perform an electron transfer working as an energy transfer agent instead. The energy transfer causes a homolysis of the N-O bond without changing the oxidation state while Cu catalysis performing the rest of the work by coordinating nucleophilic C-component and performing a reductive elimination to create a C-C bond. Another interesting detail lies in the synthetic application of these processes. The functionalized oxazolidines can be easily hydrolyzed to release both free amine and hydroxyl functionalities.

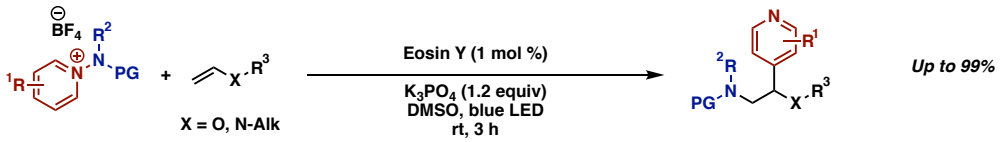


Scheme 1.27: Energy transfer photocatalysis in Umpolung two-component carboamination

Some of the reports on photocatalytic two-component carboamination describe quite peculiar application of bifunctional radical precursors to receive both N- and C-moieties from the same starting material. Like to the examples described earlier in "2e$^-$ Two-component Carboamination" paragraph[23–27], this technique allows one to obtain non-cyclic products via intermolecular radical carboaminaton. However, due to the prefabrication requirements and modularity restrictions, these reactions have to be categorized as two-component carboamination. In 2018, Feng and co-workers described a photoredox approach of alkene carboamination with enoxyphthalimides[50]. Interestingly, the radical approach allowed the authors to expand the scope towards unactivated alkenes. The reaction makes use of strongly oxidizing $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ photocatalyst to initiate the reaction by generating a phthalimidyl radical (Scheme 1.28). After a C-N bond formation, the reaction drives towards a radical chain process by intercepting another equivalent of substrate and taking the ketyl fragment alongside with the release of phthalimidyl radical. Another two-component process that unlock the access to the formal three-component products was reported by Baik and Hong[51]. The authors incorporated *N*-aminopyridimium salts as bifunctional reagents for light promoted 1,2-aminoarylation of electron rich alkenes. The reaction occurs via a radical chain mechanism and is able to functionalize a variety of vinyl ethers and enamides (Scheme 1.29).



Scheme 1.28: One-electron variation of two-component carboamination with enoxyphthalimides



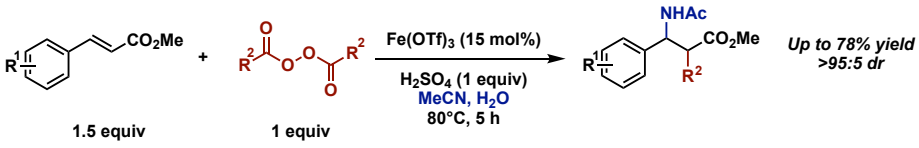
Scheme 1.29: *N*-aminopyridinium bifunctional reagents for carboamination

Although the last examples require some effort to be put in the preparation of the substrates, the results are of a great importance for the study on three-component difunctionalization process. The authors were able to demonstrate the addition of the radical intermediates can occur with a high chemo- and regioselectivity without having the radical center bound to the olefin. Which proves the radical chemistry is able to unlock the access to a fully modular three-component process.

1.3.3 Three-Component Carboamination

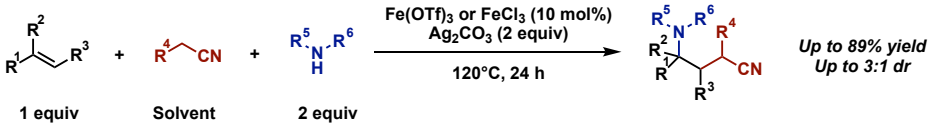
As discussed in the previous paragraphs, the genuine three-component carboamination encounters a number of chemoselectivity and regioselectivity challenges. And the literature precedents on $1e^-$ chemistry suggest the radical intermediates can be used to successfully solve these problems. Hence, during the last several years a number of

reports on fully modular three-component carboamination were published. For example, Bao and co-workers described a three-component process where organic peroxides were used as C-centered radical precursors[52]. The reaction makes use of Fe catalyst which is considered to reduce a peroxide to give a carboxyl radical. The radical extrudes CO_2 and forms a C-centered radical which undergoes the addition into a C=C bond. The reaction proceeds with the oxidation of the radical adduct to a carbocationic intermediate, which implies the electron-rich nature of the aryl fragment on the olefin. Lastly, an equivalent of nitrile solvent acts as a N-nucleophile to accomplish a Ritter-type chemistry.



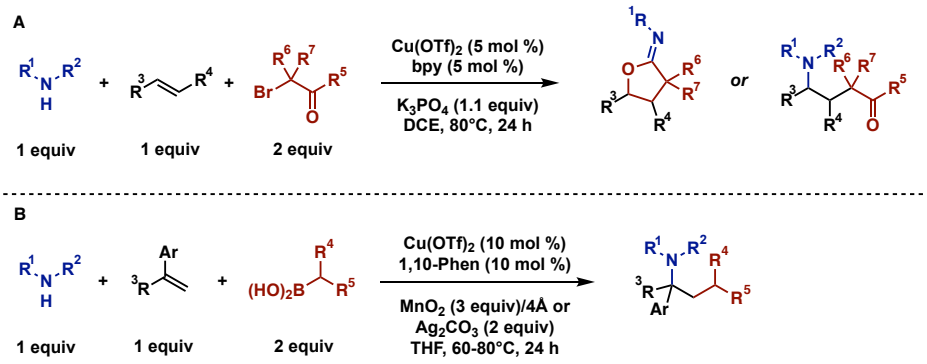
Scheme 1.30: Fe-catalyzed three-component radical carboamination

Around the same time, Li and his colleagues published a carboamination method[53] where a nitrile solvent was used as an oxidizable C-moiety source. To balance the reaction redox profile, the authors used a bulk oxidant concept described by the Chemler team and extrapolated it onto three-component process. In the paper, Ag salts were used in stoichiometric amounts to activate a nitrile molecule and oxidize it into a C-centered radical in the presence of Fe(III) catalyst. Another equivalent of Ag salt is required to generate a benzylic carbocation. The reaction was found to perform even in the absence of Fe(III), which suggests the role of Fe salt only as a Lewis acid.



Scheme 1.31: Ag-mediated oxidative three-component carboamination

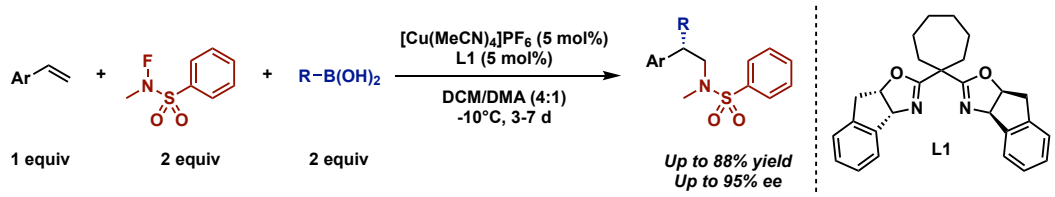
The methods by Li and Bao envisioned a true three-component reaction mode, although one of the components is used in superstoichiometric amounts and acts both as a solvent and a reagent. In 2018, the Hull group reported a fully modular three-component 1,2-carboamination of alkenes with external amine and carbon source[54]. The reaction was designed based on the ability of α-bromoesters to generate C-centered radicals in the presence of Cu compounds. Notably, the authors proposed the reaction leverages the carboxylate moiety and occurs through an oxocarbenium intermediate. This hypothesis helped the authors develop a more general platform for olefin difunctionalizaton and, for example, involve even unactivated aliphatic olefins[55,56]. Notably, the reaction was thought to proceed thought an outer-sphere mechanism rather than inner-sphere. The addition of chiral ligand could not introduce an asymmetric induction. In 2021, the Hull group also published the approach on an oxidative carboamination of olefins with boronic acids as oxidizable carbon sources[57]. Unlike the previous examples, the reaction cannot be expected to occur through an oxocarbenium intermediate, and copper is considered to play a more significant role in C-N bond formation rather than being an electron shuttle. This observation potentially unlocks the path to an asymmetrical variation of the carboamination reaction.



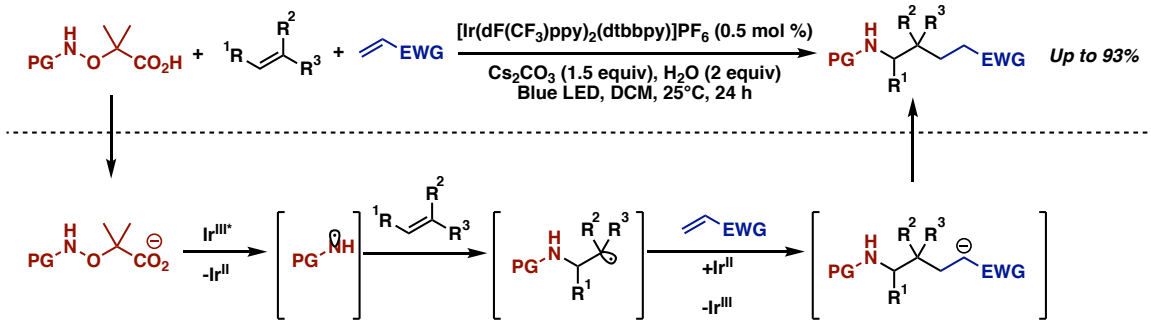
Scheme 1.32: Three-component carboamination reported by Hull and co-workers

Alongside with the carboamination through a C-centered radical addition, an opposite approach (so-called 2,1-carboamination) was also extensively investigated towards a three-component mode. In 2017, the Liu group reported an enantioselective method of carboamination through the Cu-catalyzed activation of N-F bonds in electrophilic nitrogen sources, such as NFSI[58]. Due to the high reactivity of N-centered radical, the addition step is very facile. Cu(I) catalyst is combined with a chiral BOX-family ligand to achieve high enantioselectivity. A variety of boronic acids can be used for transmetallation onto a Cu-chiral ligand complex to accomplish a C-C bond formation and deliver a product. Studer and his group used a different strategy to generate N-centered radicals[59]. Their approach requires a photoredox fragmentation of functionalized 2-oxycarboxylates which leads to the CO_2 and acetone evolution and produces a desirable N-radical. Interestingly, the system operates two possible π-acceptors, with only one of them being able to efficiently intercept N-radicals. The addition of electrophilic N-radical is favored more in case of aliphatic alkene rather than a Michael acceptor. The radical adduct formed after the addition to an aliphatic alkene is nucleophilic, thus, it is more likely to react with electron-deficient olefin. A number of different variations for radical two- and

three-component 1,2- and 2,1-alkene functionalization (including carboamination) have been recently developed further and comprehensively reviewed[3,31].



Scheme 1.33: Umpolung enantioselective three-component radical carboamination



Scheme 1.34: Radical relay three-component carboamination with Michael acceptors

1.4 Conclusion

During the last two decades, a significant progress in three-component carboamination development has been made. Various strategies, such as removable directing groups, were offered to in increase the efficiency of conventional metal complex catalysts and to avoid prefunctionalization. Moreover, a $1e^-$ chemistry was demonstrated to be a powerful tool to solve the chemo- and regioselectivity. Photoredox catalysis made a dramatic way from just a laboratory curiosity to emerging as a valuable method to explore unusual and unknown reactivities and expanding the scope of possible substrates for difunctinalization. A huge advancement has been made for the development of racemic

systems. Given the potential application of N-containing molecules in pharmaceutical industry, agrochemistry and medicine, an urgent demand for the products that possess pharmacophore functionalities, especially the ones that can be synthesized via asymmetric variations of carboamination reactions, is still not satisfied. Herein, the attempts to address these challenges and expand the application of fully intermolecular three-component 1,2-carboamination are reported.

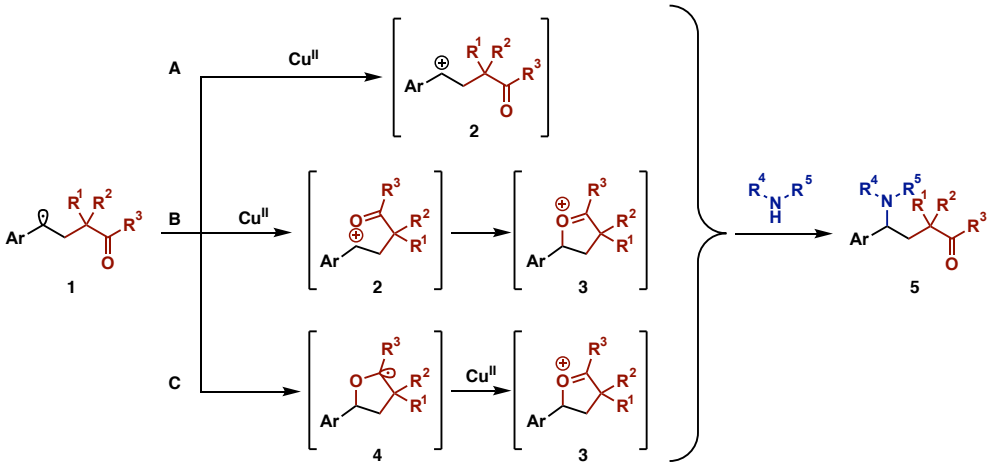
CHAPTER 2. CU-CATALYZED THREE COMPONENT CARBOAMINATION OF 2-ARYLACRYLATES.

2.1 Background

In 2018 and 2021, the Hull group reported a series of works on three-component carbofunctionalization of olefins, mainly carboamination reaction with amines and α-halocarbonyls[54,55]. The reaction is catalyzed by copper/2,2'-bipyridine (or other nitrogen containing ligand) and was demonstrated to involve a broad scope or secondary amines, such as derivatives of *N*-methylaniline, carbazole, indoline and many others. Although the transformation allows one to synthesize complex frameworks within one step, it has some directions for improvement. The first limitation arises from the olefin scope which is mostly represented by various vinylarenes and vinylheteroarenes. The presence of an aromatic system in the olefin moiety is a crucial factor for the intermediates stabilization that allows one to not apply harsh conditions, such as very high temperatures, for the substrate to react. A potential expansion of the reaction onto 1,2-carboamination of α,β-unsaturated carbonyls, carboxylic acids and their derivatives is of a great interest from both synthetic and mechanistic perspectives. First, the resulting unnatural α-aminoacid derivatives are attractive for their potential biological activity. This reaction is also based on an interesting strategy of f α-carbon functionalization with a nucleophilic amine source, which seems an unusual approach due to the insufficient electrophilic character of α-carbon atom in α,β-unsaturated carbonyls.

For better understanding of the second limitation of the original carboamination work, we should refer to a proposed reaction mechanism (Scheme 2.1). It originates from the nature of intermediates that are being formed in course of the reaction and connected with the immediate involvement of electrophile fragment. After the addition of tertiary

radical formed from α-halocarbonyl, a (pseudo)benzylic radical adduct **1** is formed. These species are proposed to undergo next steps in different manners.



Scheme 2.1: Formation of oxocarbemium intermediates

The first option – path **A** – is an oxidation process to form a (pseudo)benzylic carbocation **2** that is being attacked by an amine to form a C-N bond. The carbocation formed can rely solely on the stabilizing (or destabilizing) interactions that originate from the presence of (hetero)aryl group and the character of substituents attached to it. Path **B** implies an alternative way to a cationic intermediate formation. In this case, the C=O bond of the carboxylic group participates to form a cyclic oxocarbenium intermediate **3**. The evidence for oxocarbenium **3** were the formation of lactone side product and a very peculiar behavior of primary amines, such as anilines[54]. If the olefin has election donating groups in the aromatic ring, the reaction leads to a linear carboamination product **5**. This pathway likely occurs through a stable open shell carbocationic intermediate **2**, like in first option, and C=O bond participation is not necessary. However, if there are no strong election donors in the aromatic ring, the reaction gives predominantly an iminolactone. The

formation of iminolactone can be expected due to a nucleophilic attack occurring onto a carbonyl group instead of oxocarbenium ring opening. These two observations suggest that the formation of oxocarbenium intermediate **3** is a key step that dictates the reaction path and should be taken into consideration when transferring to other olefin classes, such as election deficient olefin. Lastly, path **C** is a variation of oxocarbenium formation where the radical adduct undergoes a cyclization through a radical addition over C=O bond. The resulting radical intermediate **4** is very electron rich, thus, it should be capable of reducing an oxidized state of Cu catalyst. The formation of such cyclic radical intermediates was postulated by Lei [60,61] and Nishikata[45].

Given the intermediates proposed for the plausible mechanism of the reaction, we see that C=O bond fragment of electrophile is expected to be deeply integrated in the mechanism. This feature allows to produce the products from substrates with an internal C=C bond with great diastereoselectivity. At the same time, electrophile scope is restricted mainly to α-halocarbonyls, with some examples of sulfone-based electrophiles described. Noteworthy, no evidence for the copper mediated C-N bond formation was obtained. The experiments with chiral ligands demonstrated dramatically low *e.e.* values for the carboamination product. The lack of significant asymmetric induction level can serve as an argument against the direct involvement of the copper complex into the amination step[54,55].

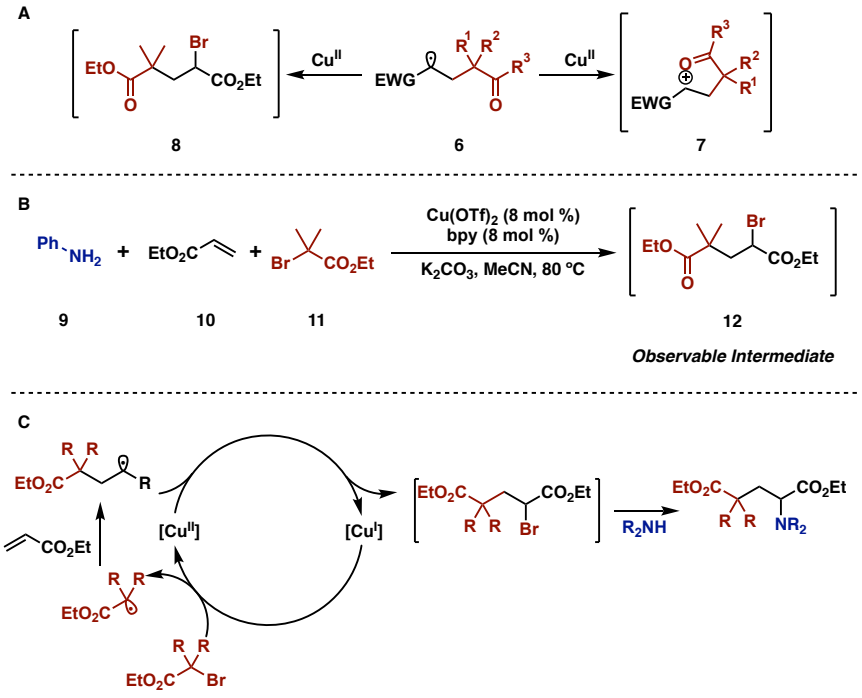
To sum up, the reaction has a vast potential for improvement. The development of enantio- and diastereoselective variations of three-component carboamination seems a reasonable step in the studies on this reaction. Changing the olefin model may be a solution for this problem. The further studies will probably require the use of a different substrate family which is more suitable for a direct involvement of catalyst in the amination step.

Having a proper metal-carbon bound intermediate formed, one should be able to tune the enantio- and diastereoselectivity with certain chiral ligand.

2.2 Project Design and Preliminary Studies

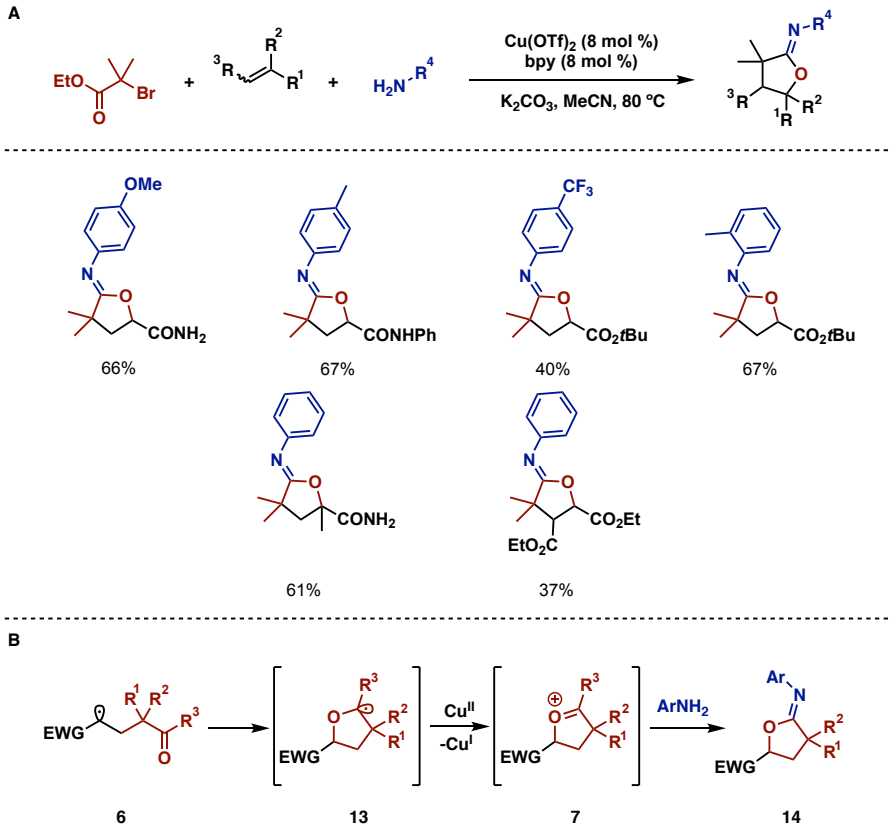
Earlier in our group we explored a possibility of using electron deficient olefins, like α,β-unsaturated carbonyls, esters and their derivatives, as substrates (Scheme 2.2). The three-component carboamination of these substrates may be a powerful technique to construct a broad range of unnatural α-aminoacid derivatives which are expected to exhibit biological activity. This class of olefins is also of a great interest from a mechanistic perspective because they are unlikely expected to form cationic intermediates, such as an "open-shell" species **7**. The electronic withdrawing group makes the formation of such species disadvantageous. Instead of that the radical adduct is expected to attach the bromine atom from the electrophile to form an atom transfer radical addition (ATRA) intermediate **8** [54,56]. The ATRA intermediate is expected to undergo a nucleophilic substitution to install the amine component.

Indeed, the preliminary studies on the carboamination of α,β-unsaturated carboxylates, performed by Ms. Grace Trammel and Dr. Daniel Kohler, revealed that the ATRA intermediate **12** is being accumulates during the first several hours in course of the reaction. The initial formation and the subsequent consumption of the ATRA intermediate within 2 h, alongside with the formation of the carboamination product, allowed us to propose that it is the key intermediate that allows the electron deficient olefins to be involved in the carboamination. The studies where the authentic ATRA intermediate was subjected to the reaction conditions revealed that both cooper catalyst and base are required for the product to be delivered.



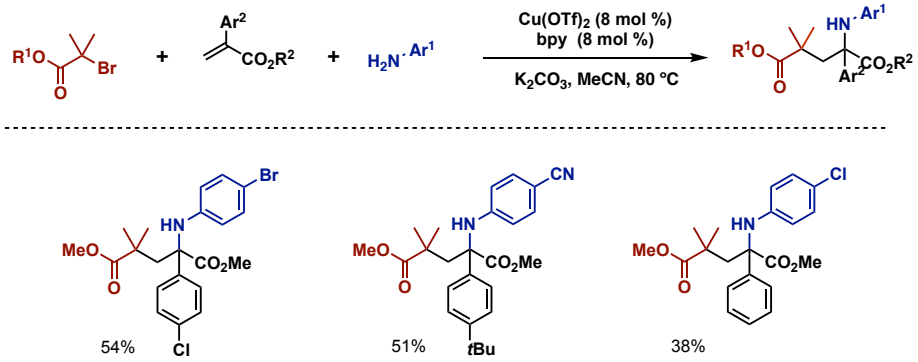
Scheme 2.2: Initial mechanistic hypothesis

The preliminary substrate scope studies revealed several interesting aspects of this reaction (Scheme 2.3). First, when using primary amines, such as aniline derivatives, acrylates tend to form iminolactones **14** instead of expected carboamination products. Apparently, the radical adduct **6** undergoes cyclization to give a 5-membered cycle **13**. The spin density of this intermediate is localized on an electron-rich carbon, making it more prone to be oxidized by Cu(II) to give a cationic intermediate **7**. Next, aniline acts as a nucleophile attacking the positively charged carbon to install the amine component.

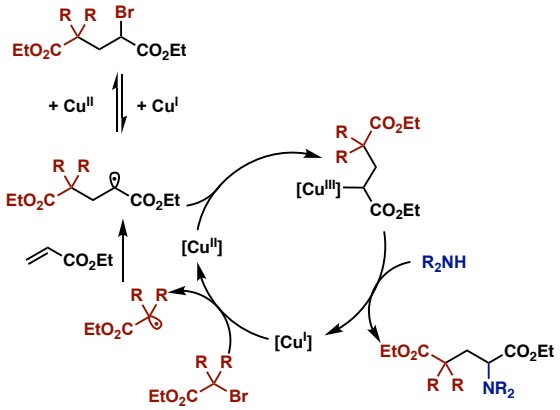


Scheme 2.3: Iminolactone formation hypothesis

Another curious observation was made when 2-arylacrylates were used for difunctionaization (Scheme 2.4). These derivatives were found to form desirable carboamination products with moderate yields. This observation contradicts with the proposal that the amination step may occur via S_N2-attack of the nucleophilic amine because the target carbon is too hindered for S_N2 to occur. Thus, another hypothesis was proposed, where ATRA intermediate exists in equilibrium with electrophile-olefin radical adduct (Scheme 2.5). This adduct may be potentially involved in Cu-mediated amination to afford carboamination product.



Scheme 2.4: Initial results on carboamination of 2-arylacrylates



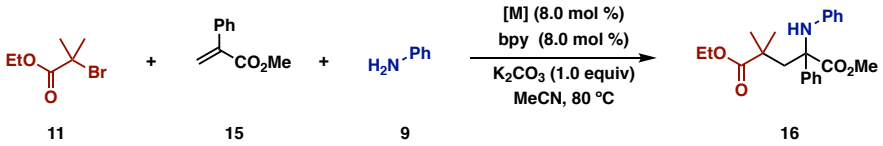
Scheme 2.5: Generic carboamination mechanism hypothesis

Overall, 2-arylacrylates can serve as an interesting model to study the possibility of using olefin with electron-withdrawing groups as substrates for 1,2-carboamination and to gain a deeper understanding of the reaction mechanism. Cu-mediated amination step and potential involvement of chiral catalyst for asymmetric carboamination are also of a great interest. Lastly, this modification of the carboamination may be a potent tool in synthesis of sterically hindered amines and branched unnatural α-aminoacid derivatives.

2.3 Three-Component Carboamination of 2-arylacrylates. Reaction Development

General conditions applied for the synthesis of iminolactones were used as a starting point. Methyl atropate **15** was used as a model substrate. Aniline **9** and ethyl α-bromoisobutyrate **11** served as a model nucleophile and a model electrophile respectively. The first phase of parametrization studies was performed in a diversification manner to probe how the system behaves when a certain parameter – metal source, ligand, solvent, base – deviates from a starting point. Metal source screen was performed first.

Table 2.1. Selected metal source screening results for three-component atropate carboamination[a]



11 15 9 16

Entry	M	Yield, %[b]
1	$Cu(OTf)_2$	45
2	CuCl	58
3	CuBr	57
4	$CuCl_2$	52
5	$Fe(OTf)_2$	8
6	$Fe(OTf)_3$	3
7	$CoCl_2$	0
8	$NiCl_2$	2
9	$NiBr_2$	3

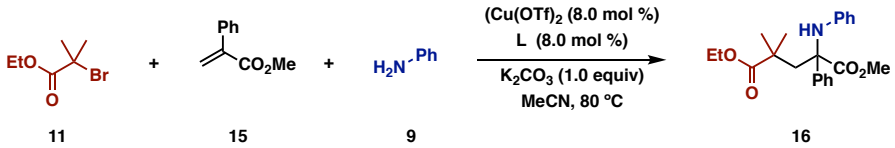
[a]See SI for experimental details. [b]Yield determined by GC analysis.

Gratifyingly, starting conditions delivered the desirable product **16** with moderate yields and high chemoselectivity. Cu(I) sources (Table 2.1, Entries 2-3) were found to

perform better than their Cu(II) analogs (Table 2.1, Entries 1,4). Noteworthy, copper was the only metal able to deliver the product **16** with the yields from moderate and higher, whereas cobalt, nickel and iron salts were found to be poorly applicable (Table 2.1, Entries 5-9). The structure of **16** was established by NMR spectroscopy and X-Ray crystallography.

Ligand screen was the next logical step in the reaction development. Various bidentate N-binding ligands such as 2,2'-bipyrinide (bpy) and 1,10-phenanthroline derivatives were examined as well as polydentate N-binding ligands (Table 2.2). Among the ligands screened, the combination of $Cu(OTf)_2$/2,2'-bipyridine (Entry 1) were found to give one of the best yields. 1,10-Phenanthroline (Entry 2) and TMEDA (Entry 5) turned out to exhibit on par with bpy family, activity. Noteworthy, the ligands with 2 and more binding sites, such as Terpy, TPA, TPEN, performed significantly worse (Entries 3, 4, 6). These data may indicate the catalyst is sensitive to the number of free available coordination sites on and inner-sphere mechanism is more likely to take step than the outer-sphere. Cu/ligand ratio studies demonstrated the reaction yields start to level up after 1:1 ratio. When 8 mol % $Cu(OTf)_2$ were used, 10 mol % or 15 mol % did not lead to a significant increase in yields (Entries 7, 8). The control reactions performed in the absence of metal source, ligand or both demonstrated they are the important pieces for the catalytic system to work (Entries 9-11).

Table 2.2. Selected ligand screening results for three-component atropate carboamination[a]



11 15 9 16

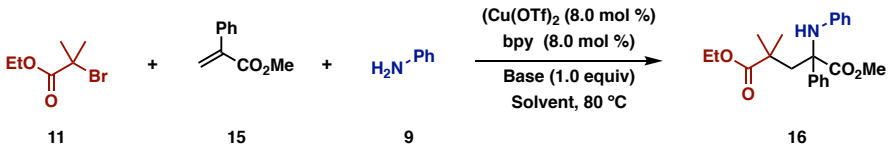
Entry	Ligand	Ligand loading, mol %	Yield, %[b]
1	bpy	8	45
2	Phen	8	48
3	Terpy	8	34
4	TPA	8	29
5	TMEDA	8	51
6	PMDTA	8	31
7	bpy	10	47
8	bpy	15	48
9	bpy	0	22
10[c]	–	0	0
11[c]	bpy	8	0

[a]See SI for experimental details. [b]Yield determined by GC analysis. [c]No Cu added.

Other parameters, including various solvents, bases were screened (Table 2.3). Acetonitrile was found to be the best solvent for the reaction (Entry 1). 1,2-dichloroethane (Entry 2) and ethereal solvents, such as dimethoxyethane (Entry 3), 1,4-dioxane (Entry 5) and tetrahydrofuran (Entry 4), performed worse. Also, the reaction was found to depend on the nature of the cationic moiety of the base. When potassium salts were used (Entries 6-10), the yields of **16** varied from very low to moderate. Potassium carbonate was shown to be the best. Potassium phosphate performed slightly worse. Fluoride and organic anions, such as alkoxides and carboxylates, were inefficient. When sodium or lithium salts were

used (Entries 11-16), the desirable product **16** was delivered with very low yields. The control reaction in the absence of base yielded no reaction.

Table 2.3. Selected solvent and base screening results for three-component atropate carboamination[a]



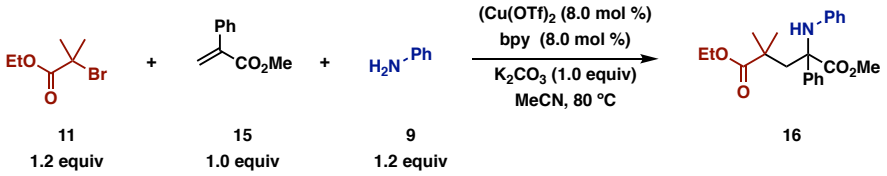
11 15 9 16

Entry	Solvent	Base	Yield, %[b]
1	MeCN	K_2CO_3	45
2	DCE	K_2CO_3	30
3	DME	K_2CO_3	34
4	THF	K_2CO_3	29
5	1,4-Dioxane	K_2CO_3	24
6	MeCN	K_2CO_3	39
7	MeCN	K_3PO_4	33
8	MeCN	KOAc	9
9	MeCN	KF	3
10	MeCN	KOMe	8
11	MeCN	Na_2CO_3	8
12	MeCN	NaOAc	3
13	MeCN	NaF	0
14	MeCN	NaOMe	9
15	MeCN	LiOAc	1
16	MeCN	LiOMe	0

[a]See SI for experimental details. [b]Yield determined by GC analysis.

When the deviations from the major reaction parameters were explored, some final adjustments were introduced via mix-and-match approach. The results on the final optimization can be found in Table 2.4. Cu(I) sources, namely CuCl (Table 2.4, Entry 3) and CuBr (Table 2.4, Entry 2) were found to be a better replacement for Cu(II) (Table 2.4, Entry 1) in terms of yields. Also, unlike Cu(II), they do not need an extra sacrificial amount of amine **9** to reduce Cu(II) to Cu(I) and launch the cycle. Ligands with electron donating groups, such as 4,4'-di-tertbutyl-2,2'-bipyridine, were not initially found to significantly increase the reaction yield. However, after a series of ligand revision, dtbbpy was considered as a promising ligand (Table 2.4, Entries 4-5). The advantage of CuCl versus CuBr is that the first one has a better solubility upon complexation with dtbbpy. Lastly, the substrate loading studies revealed the reaction responds the best when 2.0 equiv of electrophile **11** and atropate **15** are used alongside with 1.0 equiv of nucleophile **9** (Table 2.4, Entry 6).

Table 2.4. Final optimization results for three-component atropate carboamination[a]



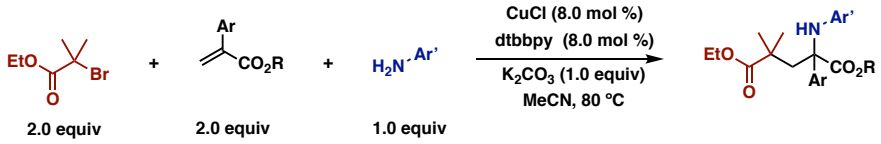
Entry	Deviation	Yield, %[b]
1	None	45
2	CuBr instead of $Cu(OTf)_2$	55
3	CuCl instead of $Cu(OTf)_2$	56
4	CuBr instead of $Cu(OTf)_2$, dtbbpy instead of bpy	64
5	CuCl instead of $Cu(OTf)_2$, dtbbpy instead of bpy	60
6[c]	CuCl instead of $Cu(OTf)_2$, dtbbpy instead of bpy	74

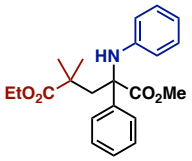
[a]See SI for experimental details. [b]Yield determined by GC analysis. [c]2.0 equiv of electrophile and atropate and 1.0 equiv of nucleophile used.

Under the optimized conditions, a wide scope of 2-arylacrylates, anilines and N-methylanilines were used for the carboamination. Table 2.5 demonstrates a broad range of functional groups, such as halides, alkoxy- and carbonyl, are tolerated under the reaction conditions. Noteworthy, the presence of bulky substituents next to the olefin's double bond does not suppress the carboaminaton. Currently, the aniline scope is represented by primary amines mostly. The anilines with *p*-substituents were demonstrated to give the corresponding products with moderate to high yields. Whereas sterically hindered anilines were found to react poorer and delivered the products with only moderate yields. Despite the high chemoselectivity and broad scope demonstrated, some of the substrates were found to provide lower yields than expected. However, the results can be used to consider

a number of interesting details from a mechanistic point of view. For example, an electron rich 2-(4-methoxyphenyl)acrylate was found to give a ~2:1 mixture of carboamination **23** and iminolactone products and was isolated with only 40% yield, whereas a substrate with a weaker EDG, such as 4-methyl-, gave exclusively a carboamination product **21** with 86% average yield. The isomers **24** and **25** with 3-MeO- and 2-MeO-groups gave the carboamination product with 61% and 64% respectively. That said, the reaction appears to be sensitive to the character of the *p*-substituent of the phenyl ring on the atropate. The electron donating character of the methoxy- group makes it push the electron density onto the a-carbon of the radical adduct. This feature makes the radical more nucleophilic and more likely to undergo a radical 5-*endo*-trig cyclization to give a cyclic radical. These species can be readily oxidized with Cu(II) into an oxocarbenium species and produce either a lactone or iminolactone product. On the other hand, having a methoxy- group installed as a *m*-substituent does not provide a necessary direct conjugation between the oxygen and the a-carbon of the radical adduct. 2-MeO-group is expected to disrupt a planar geometry required for the electronic effects to affect the benzylic carbon.

Table 2.5: Substrate scope





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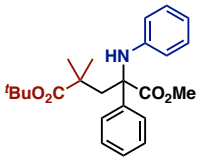

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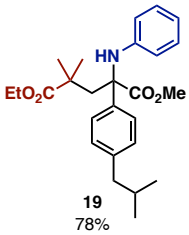

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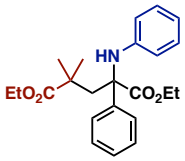

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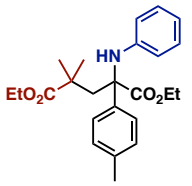

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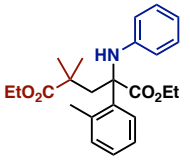

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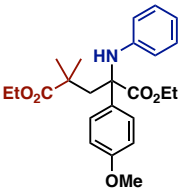

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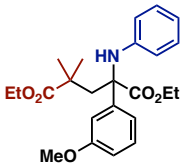

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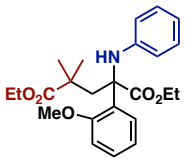

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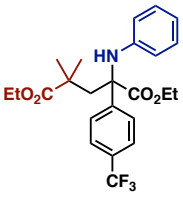

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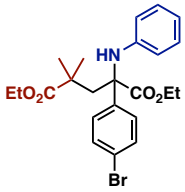

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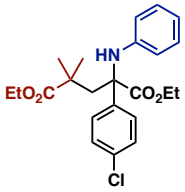

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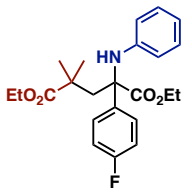

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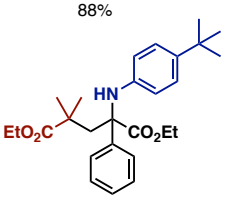

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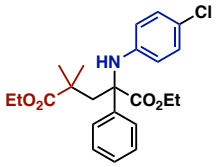

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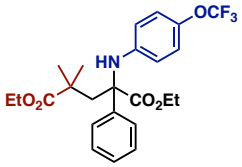

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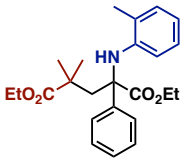

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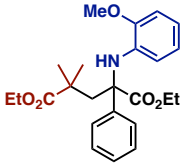

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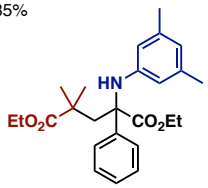

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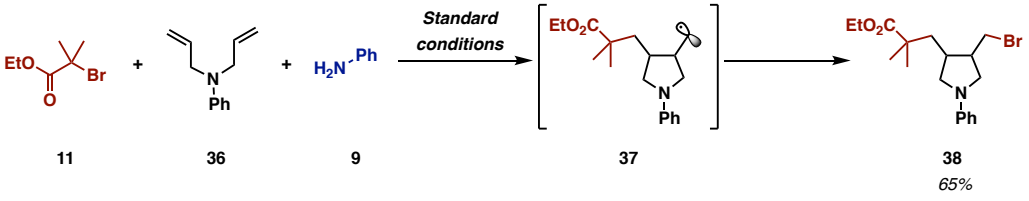
2.4 Mechanistic Studies

To better understand the mechanism of the carboamination reaction, a number of mechanistic experiments were designed and conducted. The experiments were intended to investigate the steps of the proposed catalytic cycle, including radical generation, radical addition across the C=C bond, a cycle offshoot via ATRA product formation, and C-N bond formation.

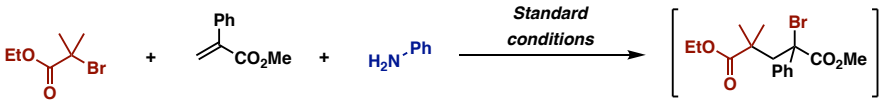
The proposed catalytic cycle is expected to start from the reduction of the electrophile to produce a carbon centered radical followed by the interception of the radical to give a radical adduct. To disclose the radical nature of these intermediates, the radical trapping experiments were performed, with *N,N*-diallylaniline acting as a trap. Earlier, we demonstrated this compound to undergo a rapid 5-*exo*-trig radical cyclization into **37** followed by bromine atom abstraction[54]. The carboamination product was not detected in this system since the oxidation of the resulting primary radical into carbocation is complicated. Partially, due to the fact the beneficial interaction with electrophile's C=O bond does not appear to take place due to geometrical properties. Instead of that, the formation of bromide **38** was detected.



Scheme 2.6: Radical trapping

Next, the probability of ATRA route was explored. As mentioned earlier, when 2-unsubstituted acrylates were used for carboamination, the accumulation of ATRA intermediate was observed within first 2 h followed by its complete consumption.

Simultaneously, upon ATRA intermediate consumption, the corresponding iminolactone product was forming. This fact may serve as an evidence that bromine atom abstraction is a crucial step for the initial stabilization of the radical intermediate followed by a cyclization to deliver an oxocarbenium intermediate (Scheme 2.2B). However, upon the transition to 2-arylacrylates, no ATRA intermediate was detected. The control experiments on ethyl atropate and ethyl α-bromoisobutyrate in the absence or with only catalytic amount of nucleophile did not deliver the corresponding ATRA product either. To deeply explore the viability of ATRA product hypothesis, we attempted to synthesize an authentic ATRA product **39**. However, the synthesis was found to be challenging due to the significant retro-Michael addition activity. A simplified model on ethyl 2-bromo-2-phenylpropanoate **40** was exploited to determine whether the presence of neighbor carboxylate is critical, and the reaction may occur through the direct amination of tertiary bromide to deliver **41**. Although a straightforward S_N2 reaction seems unviable, this process may occur via radical Ullmann amination. The studies demonstrated that CuCl/dtbbpy system can catalyze the amination, with slow background amination occurring in the absence of catalyst. The results demonstrate that in the reaction conditions the 2-bromo-2-phenyl esters behave as very reactive species which, probably, either are not formed or live long to be detected or isolated.



Scheme 2.7: ATRA product studies **(**Data obtained in collaboration with Ms. Aja M. Nicely)

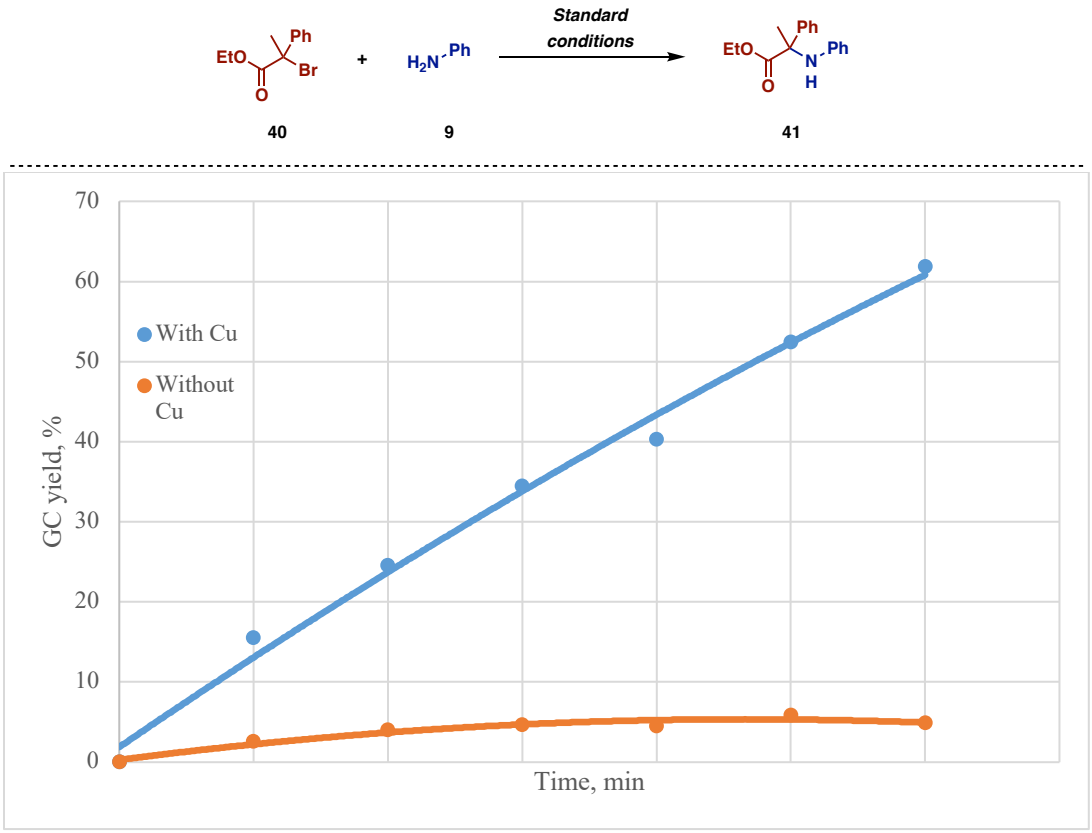
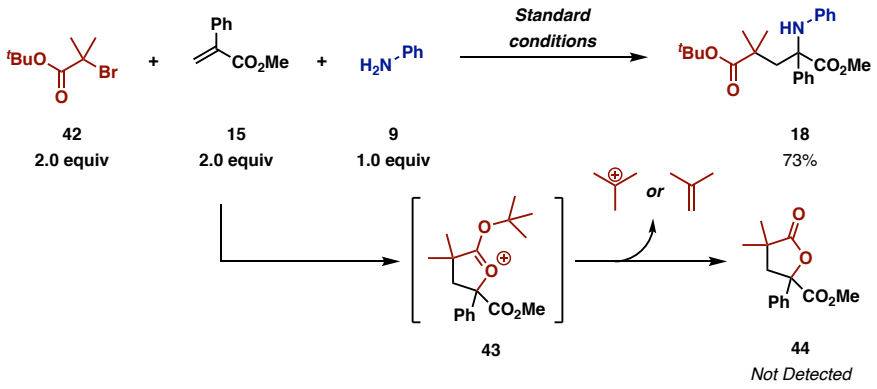


Figure 2.1: Model bromide rate studies (Data obtained in collaboration with Ms. Hannah C. Wendlandt)

To ensure our hypothesis that the carboxylate group of electrophile does not participate in the reaction via oxocarbenium intermediate formation, a *tert*-butyl α-bromoisobutyrate was used as a probe (Scheme 2.8). The choice of the electrophile may be explained by the fact it easily yields a lactone **44** via ejecting a *tert*-butyl carbocation or eliminates isobutene from upon the oxocarbenium **43**. Earlier we observed this phenomenon for carboamination of styrenes[54]. Interestingly, the experiment delivered the carboaminaton product **18** in good yield with no lactone **44** detected. This fact may indicate the carboaminaton of atropate **15** does not affect the neighboring group and does not proceed through the oxocarbenium intermediate **43**. A more active role of 2-aryl substituent

in decreasing the redox potential of the radical adduct and taming the undesirable cyclization process seems a more viable explanation, with *p*-substituents being able to modulate the philicity of the radical center.

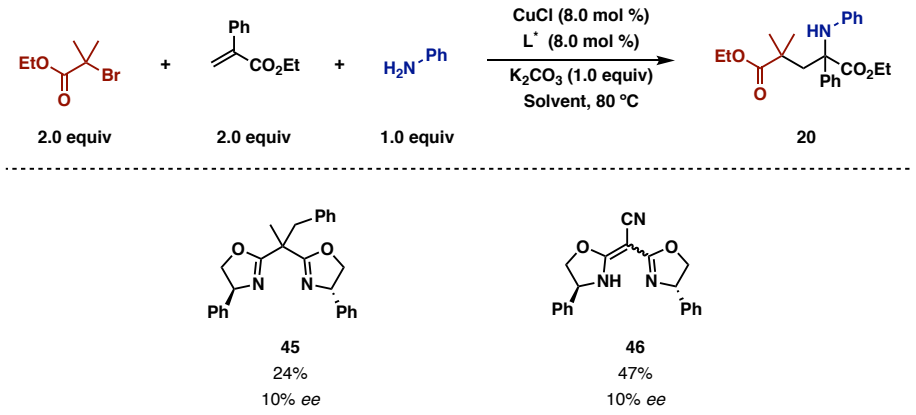


Scheme 2.8: Oxocarbenium intermediate studies

Overall, the results on the possible ATRA intermediate involvement and the behavior of certain substrates such as *tert*-butyl α-bromoisobutyrate or 2-arylacrylates with electron donating groups (such as **23**) suggest that a) the presence of aryl group on acrylate helps to decrease a redox potential of the radical center and makes the ATRA product **39** formation less necessary; b) in case of 2-unsubstituted acrylates, the oxocarbenium formation requires a Cu complex, which indicated that either a $1e^-$ redox process or a Lewis acid-catalyzed cyclization via intramolecular S_N2 substitution takes place; c) carboamination in case of 2-arylacrylates is unlikely to occur through oxocarbenium species.

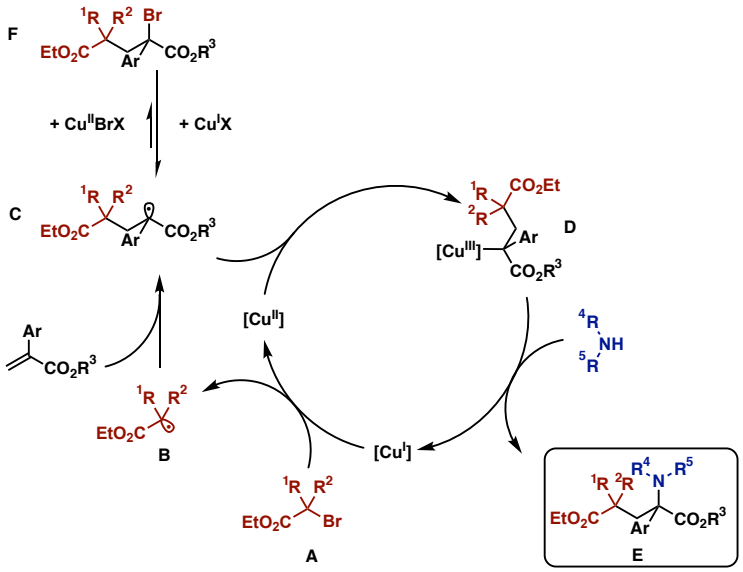
Establishing the nature of the C-N bond formation was of a greatest interest. Initially we hypothesized that due to the properties of radical adduct **6** the reaction may occur via Cu-mediated C-N bond formation. To determine if Cu catalyst is directly involved into an inner-sphere amination, a number of chiral ligands, namely from BOX

and PyBOX family, were applied (Scheme 2.9). Gratifyingly, the ligands **45** and **46** were found to introduce the asymmetric induction and deliver 10% *ee*.



Scheme 2.9: Chiral ligand screening **(**Data obtained in collaboration with Ms. Aja M. Nicely)

Taking into the consideration the results of mechanistic studies, the plausible catalytic cycle involves the following steps (Scheme 2.10). The reaction starts with the reduction of bromide **A** by Cu(I) to produce a radical **B**. Then, an addition into C=C double bond occurs to give a radical adduct **C**, which, in turn, interacts with Cu(II) species to give **D**. Upon the amine coordination, the Cu-mediated amination takes place to deliver the product **E**. The side process to produce the ATRA intermediate **F** is less likely to occur, in comparison with 2-unsubstituted acrylates.



Scheme 2.10: Mechanistic hypothesis for acrylate carboamination

2.5 Conclusion and further directions

The present work was devoted to the development of carboamination protocol of 2-arylacrylates that involves an unusual pattern of reactivity via nucleophilic amination of α-carbon. The reaction is catalyzed by Cu complex with N-containing ligand and proceeds through a radical relay mechanism. Key differences in reactivity of 2-arylacrylates versus 2-unsubstituted analogs are demonstrated. Due to the presence of the aryl group, the 2-arylacrylates family was found to exhibit a different reactivity pattern and deliver the carboamination products with excellent selectivity and moderate to high yields. The mechanistic evidence of the Cu-mediated amination and the absence of oxocarbenium intermediate are provided. Further investigations will include more in-depth studies of the reaction mechanism, such as kinetic experiments, calculations on the geometry and energy of intermediates and asymmetric induction. Expansion of the substrate scope towards various primary and secondary amines, halides and 1,1-disubstituted electron deficient alkenes and the development of an asymmetric variation of this reaction will allow to create

a platform for the rapid assembly of various chiral α-aminoacid derivatives with sterically hindered carbon atoms.

CHAPTER 3. EXPERIMENTAL

3.1 General Information

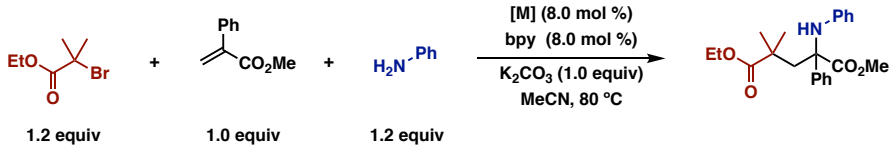
General Experimental Procedures: Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level ~ 0.1 ppm). Column chromatography was performed with silica gel from SiliCycle (40-63 μm) with a column mixed as a slurry with the eluent and was packed, rinsed, and run under increased pressure. Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator with visualization by short wave (254 nm) ultraviolet light. Distillations were performed using a 3 cm short-path column under reduced pressure.

Instrumentation: ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance NEO 400 MHz (101 MHz for ^{13}C, 376 MHz for ^{19}F), Agilent MR 400 MHz (101 MHz for ^{13}C, 376 MHz for ^{19}F), Bruker Avance III 500 MHz (126 MHz for ^{13}C, 471 MHz for ^{19}F) and Bruker AVIII HD 500 MHz (126 MHz for ^{13}C, 471 MHz for ^{19}F) spectrometers. Spectra were referenced to the residual solvent peak of $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, J, are reported in Hertz and integration is provided, along with assignments, as indicated. Gas Chromatography (GC) was performed on a Shimadzu GC-2030 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). Enantiomeric ratios were measured on Shimadzu Prominence HLPC system with SPD-M20A UV/VIS Photodiode array detector using Chiralpak IA-3, IB-3, IC-3, ID-3 columns. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS) and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated Stainless Steel columns while following manufacturer's recommendations for solvent preparation and dispensation unless otherwise noted. Acetonitrile and 1,2-Dichloroethane were purchased from Aldrich Chemical in a sure-sealed bottle, which was transferred into a glove box under nitrogen immediately upon receipt. Amines were distilled and degassed using the freeze-pump-thaw method upon receipt (unless otherwise noted) and stored under nitrogen in a glove box. Styrene was purchase from Aldrich Chemical and was washed with 5 M NaOH to remove inhibitors. It was then dried over $MgSO_4$, pulled through a plug of neutral alumina, and degassed using the freeze-pump-thaw method. It was stored at -40 °C under nitrogen in a glove box. Unless otherwise shown, all non-commercial substrates were prepared according to the known literature procedures[62–68].

3.2 Select Optimization Results

Table 3.1. Varying the Metal Salt.[a]

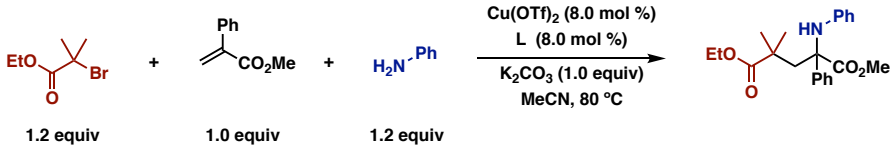


Run	[M]	pdt yield, %[b]
1	CuCl	56
2	CuBr	55
3	CuI	55
4	$[Cu(MeCN)_4]PF_6$	46
5	CuThioCarb	56
6	CuOAc	48
7	Cu(IMes)Cl	41
8	CuOTf	38
9	$CuCl_2$	52
10	$CuBr_2$	56
11	$Cu(OAc)_2$	34
12	$Cu(OTf)_2$	45
13	$Fe(OTf)_2$	8
14	$FeCl_2$	10
15	$Fe(OTf)_3$	3
16	$FeCl_3$	2
17	$Fe(acac)_3$	0
18	$CoCl_2$	0
19	$NiCl_2$	2
20	$NiBr_2$	3

21	$NiCl_2$•DME	0
22	$NiBr_2$•DME	0
23	$Ni(PPh_3)_2Cl_2$	0

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with metal salt (0.008 mmol, 0.08 equiv), K_2CO_3 (14 mg, 0.10 mmol, 1.0 equiv), and a stir bar. 0.20 mL of a MeCN stock solution containing 2,2'-bipyridine (1.25 mg, 0.008 mmol (0.040 M), 0.08 equiv) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (18 μL, 0.12 mmol, 1.2 equiv), aniline (11 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14 μL, 0.10 mmol, 1.0 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] *In situ* yield determined by GC analysis with comparison to 1-methylnaphthalene (10. μL) as an internal standard.

Table 3.2.1. Varying the Ligand.[a]

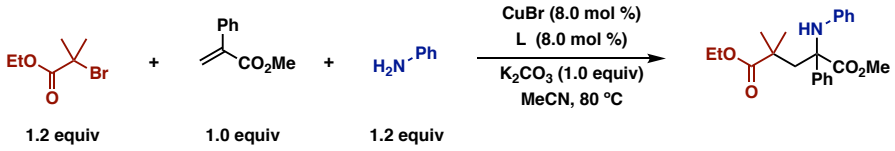


Run	Ligand	pdt yield, %[b]
1	Phen	48
2	Bathophen	49
3	Bathocuproine	35
4	Neocuproine	34
5	dOMePhen	45
6	tetraMePhen	45
7	dMe-dOMePhen	36
8	bpy	45
9	dtbbpy	47
10	dOMebpy	46
11	Terpy	34
12	TPA	29
13	TPEN	29
14	DPEPA	35
15	4-OMe-DMAMP	24
16	Py	28
17	4-OMe-Py	38
18	DMAP	46
19	2,6-Lutidine	29
20	tBuBOX	23
21	PhBOX	39
22	BnBOX	31

23	TMEDA	51
24	No Ligand	22

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with Ligand (8 μmol, 8 mol %) CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

Table 3.2.2. Varying the Ligand.[a]

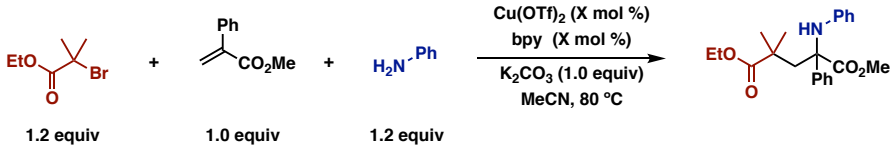


Run	Ligand	pdt yield, %[b]
1	Phen	61
2	Bathophen	54
3	Bathocuproine	41
4	Neocuproine	38
5	dOMePhen	42
6	tetraMePhen	59
7	dMe-dOMePhen	37
8	bpy	55
9	dtbbpy	64
10	dOMebpy	49
11	Terpy	29
12	TPA	29
13	TPEN	24
14	DPEPA	34
15	4-OMe-DMAMP	27
16	Py	14
17	4-OMe-Py	28
18	DMAP	33
19	2,6-Lutidine	10
20	tBuBOX	15
21	PhBOX	35
22	BnBOX	37

23	TMEDA	35
24	No Ligand	11

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with Ligand (8 μmol, 8 mol %) CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

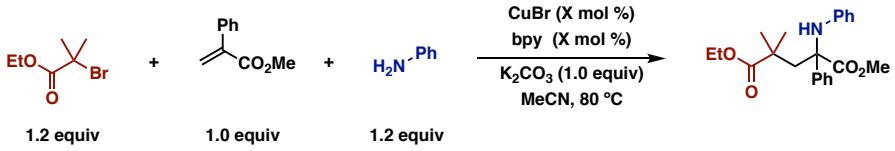
Table 3.3.1. Varying the Catalyst Loadings.[a]



Run	Catalyst loadings, mol %	pdt yield, %[b]
1	1	39
2	2	47
3	3	46
4	4	47
5	5	40
6	8	45
7	10	43
8	15	42
9	20	39

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 µL of a MeCN sock solution containing CuBr (0-20 mol %) and 2,2'-bipyridine (0-20 mol %) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 µL, 0.12 mmol, 1.2 equiv), aniline (11.0 µL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 µL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 µL) as an internal standard.

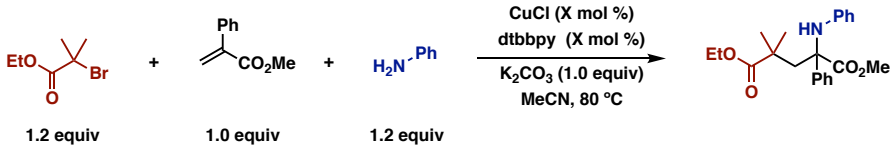
Table 3.3.2. Varying the Catalyst Loadings.[a]



Run	Catalyst loadings, mol %	pdt **1** yield, %[b]
1	1	44
2	2	51
3	3	54
4	4	54
5	5	53
6	8	55
7	10	54
8	15	55
9	20	58

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 µL of a MeCN sock solution containing CuBr (0-20 mol %) and 2,2'-bipyridine (0-20 mol %) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 µL, 0.12 mmol, 1.2 equiv), aniline (11.0 µL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 µL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 µL) as an internal standard.

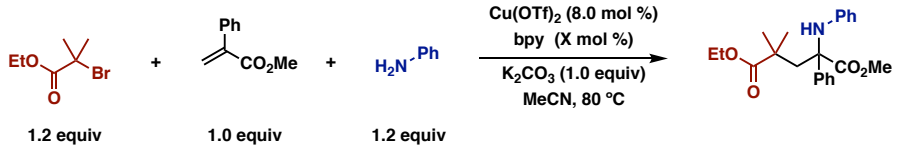
Table 3.3.3. Varying the Catalyst Loadings.[a,c]



Run	Catalyst loadings, mol %	pdt yield, %[b]
1	1	42
2	2	47
3	3	47
4	4	47
5	5	52
6	6	63
7	7	59
8	8	60
9	9	60
10	10	59

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 µL of a MeCN sock solution containing CuCl (0-20 mol %) and 4-4'dimethyl-2,2'-bipyridine (0-20 mol %) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 µL, 0.12 mmol, 1.2 equiv), aniline (11.0 µL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 µL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 µL) as an internal standard. [c.] Data obtained in collaboration with Ms. Aja M. Nicely

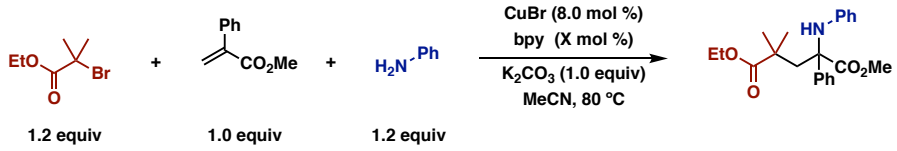
Table 3.4.1. Varying the Cu/Ligand Ratio.[a]



Run	bpy loadings, mol %	pdt yield, %[b]
1	0	22
2	1	33
3	5	44
4	8	45
5	10	47
6	15	48
7	20	45

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of a MeCN stock solution containing 2,2'-bipyridine (0-20 mol %) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

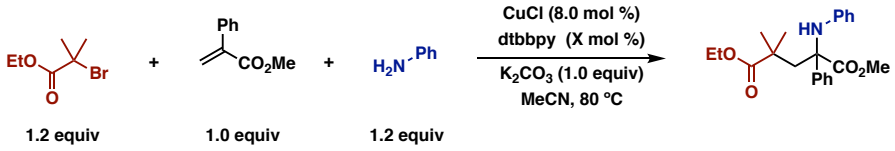
Table 3.4.2. Varying the Cu/Ligand Ratio.[a]



Run	bpy loadings, mol %	pdt yield, %[b]
1	0	11
2	1	36
3	5	49
4	8	55
5	10	59
6	15	59
7	20	62

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of a MeCN stock solution containing 2,2'-bipyridine (0-20 mol %) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

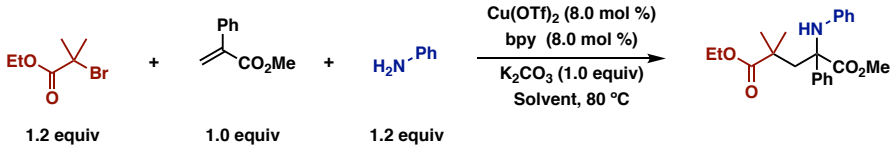
Table 3.4.3 Varying the Cu/Ligand Ratio.[a]



Run	dtbbpy loadings, mol %	pdt yield, %[b]
1	1	37
2	2	41
3	5	48
4	8	60
5	10	65
6	15	61
7	20	65

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with CuCl (0.8 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of a MeCN stock solution containing 4,4'-dimethyl-2,2'-bipyridine (1-20 mol %) was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

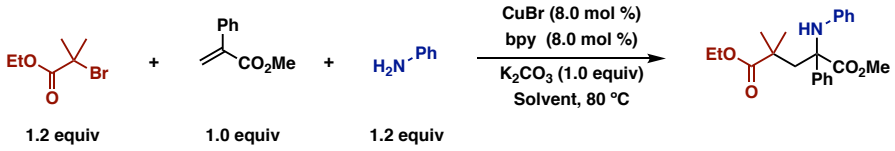
Table 3.5.1 Varying the Solvent. [a]



Run	Solvent	pdt yield, %[b]
1	DCM	38
2	DCE	30
3	MeCN	45
4	DME	34
5	Dioxane	24
6	THF	29
7	DMF	32
8	DMA	30
9	DMSO	11
10	Toluene	29

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 2,2'-bipyridine (1.25 mg, 8 μmol, 8 mol %) CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of solvent was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

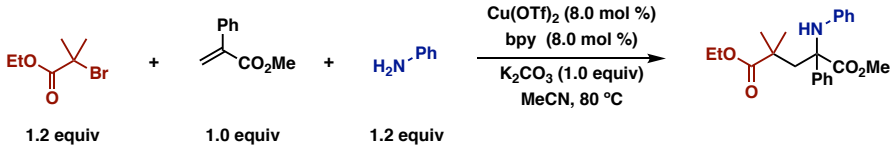
Table 3.5.2 Varying the Solvent. [a]



Run	Solvent	pdt yield, %[b]
1	DCM	2
2	DCE	2
3	MeCN	55
4	DME	51
5	Dioxane	49
6	THF	46
7	DMF	40
8	DMA	25
9	DMSO	21
10	Toluene	12

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 2,2'-bipyridine (1.25 mg, 8 μmol, 8 mol %) CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of solvent was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

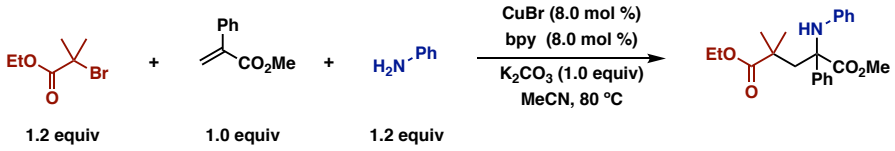
Table 3.6.1 Varying the Concentration. [a]



Run	Concentration, M	pdt **1** yield, %[b]
1	0.25	40
2	0.33	41
3	0.5	45
4	1	41
5	1.25	37

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 2,2'-bipyridine (1.25 mg, 8 μmol, 8 mol %) CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200-1000 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

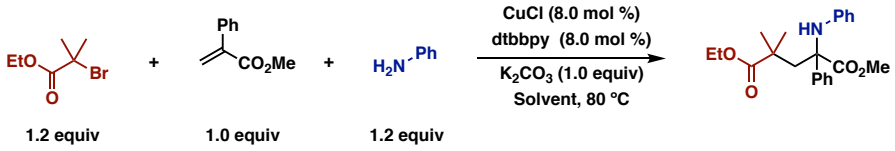
Table 3.6.2 Varying the Concentration. [a]



Run	Concentration, M	pdt **1** yield, %[b]
1	0.1	19
2	0.2	46
3	0.3	52
4	0.4	54
5	0.5	55

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 2,2'-bipyridine (1.25 mg, 8 μmol, 8 mol %) CuBr (1.15 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200-1000 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

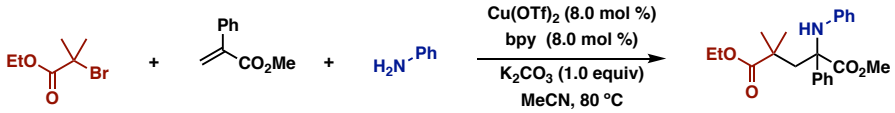
Table 3.6.3 Varying the Concentration. [a]



Run	Concentration, M	pdt **1** yield, %[b]
1	0.1	46
2	0.2	53
3	0.3	54
4	0.4	56
5	0.5	60

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 4,4'-dimethyl-2,2'-bipyridine (2.15 mg, 8 μmol, 8 mol %) CuCl (0.8 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200-1000 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (17.6 μL, 0.12 mmol, 1.2 equiv), aniline (11.0 μL, 0.12 mmol, 1.2 equiv), and methyl atropate (14.4 μL, 0.1 mmol, 1 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

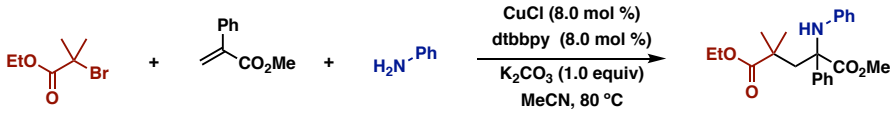
Table 3.7.1 Varying the substrate loadings. [a]



Run	Nucleophile loadings, eq	Olefin loadings, eq	Electrophile loadings, eq	pdt yield, %[b]
1	1	1	1.2	44
2	2	1	1.2	50
3	3	1	1.2	49
4	1.2	1	1.2	45
5	1.2	2	1.2	51
6	1.2	3	1.2	49
7	1.2	1	1	44
8	1.2	1	2	50
9	1.2	1	3	49

[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 4,4'-dimethyl-2,2'-bipyridine (2.15 mg, 8 μmol, 8 mol %) CuCl (0.8 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (1-1.2 equiv), aniline (1-1.2 equiv), and methyl atropate (1-4 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

Table 3.7.2 Varying the substrate loadings. [a]



Run	Nucleophile loadings, eq	Olefin loadings, eq	Electrophile loadings, eq	pdt yield, %[b]
1	1	1	1	61
2	1	2	1	61
3	1	2	2	74
4	1.2	1	1.2	60
5	1.2	2	1.2	66
6	1.2	3	1.2	64
7	1.2	4	1.2	62

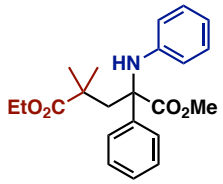
[a.] In a nitrogen-filled glovebox an oven-dried 4-mL reaction vial was charged with 4,4'-dimethyl-2,2'-bipyridine (2.15 mg, 8 μmol, 8 mol %) CuCl (0.8 mg, 8 μmol, 8 mol %), K_2CO_3 (13.8 mg, 0.1 mmol, 1 equiv), and a stir bar. 200 μL of MeCN was added. This was followed by ethyl 2-bromo-2-methylpropanoate (1-1.2 equiv), aniline (1-1.2 equiv), and methyl atropate (1-4 equiv). The vial was sealed with a Teflon-coated screw cap, removed from the glovebox, and stirred at 650 rpm at 80 °C for 24 h. [b.] In situ yield determined by GC analysis with comparison to 1-methylnaphthalene (10 μL) as an internal standard.

3.3 Experimental Procedure, Isolation, and Characterization

General Experimental Procedure

In a nitrogen-filled glove box, an oven-dried 4 mL reaction vial was charged with K_2CO_3 (27.6 mg, 0.200 mmol, 1.0 equiv), and a stir bar. Next, 400 mL of a CH_3CN stock solution containing 4,4'-dimethyl-2,2'-bipyridine (0.04 M, 16 mmol, 8.0 mol %) and CuCl (0.04 M, 16 mmol, 8 mol %) was added. Following addition of the other reagents in the general order of addition: acrylate, aniline, then bromide (see below), the vial was sealed with a Teflon-lined cap, removed from the glove box, and heated at 80 °C with stirring at 900 rpm for 24 h.

1-ethyl 5-methyl 2,2-dimethyl-4-(phenylamino)-4-phenylpentanedioate (17)



Following the general procedure above, methyl 2-phenylacrylate (57.6 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 10% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (47.9 mg, 65%).

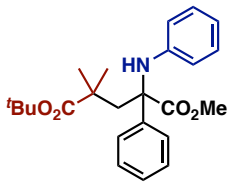
R_f= 0.28 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m, 2H), 7.24 (dt, *J* = 27.2, 7.4 Hz, 3H), 6.90 (t, *J* = 7.7 Hz, 2H), 6.52 (t, *J* = 7.3 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 2H), 5.55 (s, 1H), 3.77 – 3.65 (m, 1H), 3.64 (s, 3H), 3.20 (d, *J* = 14.3 Hz, 1H), 2.88 (d, *J* = 14.3 Hz, 1H), 2.81 (dq, *J* = 10.3, 7.1 Hz, 1H), 1.26 (s, 4H), 1.17 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.76, 175.26, 144.24, 140.28, 128.76, 128.31, 127.70, 126.89, 116.99, 115.25, 64.35, 60.01, 53.24, 43.73, 41.00, 29.47, 22.33, 14.02.

IR (ATR): 3418, 3392, 2980, 1721, 1601, 1505, 1269, 1138, 744, 689 cm^{-1}

1-tert-butyl 5-methyl 2,2-dimethyl-4-(phenylamino)-4-phenylpentanedioate (18)



Following the general procedure above, methyl 2-phenylacrylate (57.6 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and tert-butyl 2-bromo-2-methylpropanoate (70.9 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 10% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (57.7 mg, 73%).

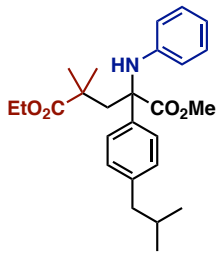
R_f = 0.36 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.38 (m, 2H), 7.26 – 7.15 (m, 3H), 6.94 – 6.88 (m, 2H), 6.53 (t, *J* = 7.3 Hz, 1H), 6.30 – 6.25 (m, 2H), 5.66 (s, 1H), 3.63 (s, 3H), 3.04 (d, *J* = 14.3 Hz, 1H), 2.85 (d, *J* = 14.3 Hz, 1H), 1.18 (s, 3H), 1.16 (s, 9H), 1.13 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.69, 175.59, 145.06, 140.47, 128.52, 128.33, 127.53, 127.22, 117.30, 116.12, 80.27, 64.99, 53.15, 44.00, 42.10, 28.68, 27.70, 23.41.

IR (ATR): 3380, 2960, 1716, 1607, 1446, 1136, 756, 692 cm^{-1}

1-ethyl 5-methyl 4-(4-isobutylphenyl)-2,2-dimethyl-4-(phenylamino)pentanedioate (19)



Following the general procedure above, methyl 2-phenylacrylate (88.6 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 10% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (66.4 mg, 78%).

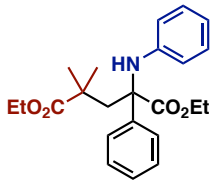
R_f = 0.30 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.89 (t, *J* = 7.7 Hz, 2H), 6.51 (t, *J* = 7.3 Hz, 1H), 6.21 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 1H), 3.69 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.64 (s, 3H), 3.18 (d, *J* = 14.3 Hz, 1H), 2.86 (d, *J* = 14.3 Hz, 1H), 2.80 (dq, *J* = 9.8, 6.8 Hz, 1H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.85 – 1.75 (m, *J* = 7.2, 6.6 Hz, 1H), 1.25 (s, 3H), 1.16 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 4H), 0.84 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.82, 175.39, 144.33, 141.16, 137.46, 129.47, 128.22, 126.60, 116.89, 115.27, 64.16, 59.97, 53.17, 45.05, 43.79, 40.99, 30.19, 29.47, 22.45, 22.43, 22.31, 14.02.

IR (ATR): 3411, 2956, 1720, 1600, 1504, 1270, 1139, 742, 689 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(4-(trifluoromethyl)phenyl)pentanedioate (20)



Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 10% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (59.0 mg, 77%).

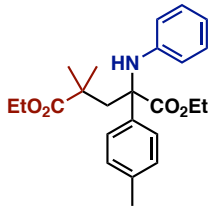
R_f = 0.35 (10% ethyl acetate in hexanes)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 7.5 Hz, 2H), 7.30 – 7.16 (m, 2H), 6.90 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.52 (t, *J* = 7.3 Hz, 1H), 6.22 (d, *J* = 8.1 Hz, 2H), 5.56 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.66 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.20 (d, *J* = 14.3 Hz, 1H), 2.89 (d, *J* = 14.3 Hz, 1H), 2.77 (dq, *J* = 10.8, 7.1 Hz, 1H), 1.23 (d, *J* = 31.0 Hz, 6H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.78, 174.63, 144.34, 140.41, 128.66, 128.27, 127.59, 126.90, 116.93, 115.29, 64.42, 62.36, 59.96, 43.69, 41.07, 29.58, 22.42, 14.03, 13.76.

IR (ATR): 3401, 2992, 1717, 1599, 1504, 1269, 1143, 749, 693 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(p-tolyl)pentanedioate (21)



Following the general procedure above, ethyl 2-(4-tolyl)acrylate (75.3 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (68.4 mg, 86%).

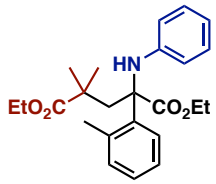
R_f = 0.26 (10% ethyl acetate in hexanes)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.91 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.52 (t, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 8.1 Hz, 2H), 4.13 – 4.03 (m, 2H), 3.66 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.18 (d, *J* = 14.3 Hz, 1H), 2.86 (d, *J* = 14.3 Hz, 1H), 2.78 (dq, *J* = 10.7, 7.1 Hz, 1H), 2.28 (s, 3H), 1.26 (s, 3H), 1.18 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.84, 174.75, 144.41, 137.33, 137.22, 129.39, 128.24, 126.76, 116.87, 115.33, 64.24, 62.30, 59.94, 43.69, 41.07, 29.58, 22.44, 21.15, 14.03, 13.80.

IR (ATR): 3399, 2985, 1716, 1600, 1504, 1268, 1143, 743, 694 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(o-tolyl)pentanedioate (22)



Following the general procedure above, ethyl 2-(2-tolyl)acrylate (75.3 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (62.3 mg, 79%).

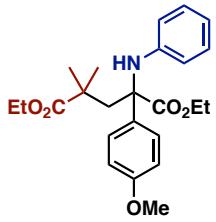
R_f = 0.29 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.16 (td, *J* = 7.4, 1.2 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.89 (t, *J* = 7.9 Hz, 2H), 6.53 (t, *J* = 7.3 Hz, 1H), 6.24 (d, *J* = 7.9 Hz, 2H), 5.30 (s, 1H), 4.16 (qt, *J* = 7.1, 3.8 Hz, 2H), 3.71 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.38 (d, *J* = 13.9 Hz, 1H), 2.84 – 2.72 (m, 2H), 2.13 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.81, 173.85, 144.42, 138.18, 137.21, 132.92, 128.28, 127.79, 127.61, 126.40, 116.85, 113.97, 64.27, 62.30, 59.96, 46.32, 41.01, 30.15, 22.27, 21.09, 14.00, 13.89.

IR (ATR): 3405, 2989, 1722, 1599, 1506, 1268, 1142, 746, 694 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(4-methoxyphenyl)pentanedioate (23)



Following the general procedure above, ethyl 2-(4-methoxyphenyl)acrylate (78.3 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (33.1 mg, 40%).

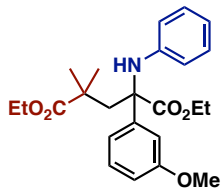
R_f = 0.19 (10% ethyl acetate in hexanes)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.91 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.52 (t, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 8.0 Hz, 2H), 5.51 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.66 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.16 (d, *J* = 14.3 Hz, 1H), 2.85 (d, *J* = 14.3 Hz, 1H), 2.77 (dq, *J* = 10.8, 7.1 Hz, 1H), 1.25 (s, 4H), 1.17 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.81, 174.80, 158.89, 144.43, 132.33, 128.28, 128.10, 116.82, 115.31, 113.99, 63.95, 62.27, 59.95, 55.28, 43.76, 41.08, 29.55, 22.42, 14.03, 13.83.

IR (ATR): 3398, 2891, 1717, 1599, 1503, 1260, 1145, 1037, 837, 743, 692 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(3-methoxyphenyl)pentanedioate (24)



Following the general procedure above, ethyl 2-(3-methoxyphenyl)acrylate (78.3 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (50.7 mg, 61%).

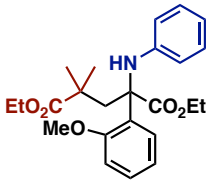
R_f= 0.24 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.97 (t, *J* = 2.2 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 2H), 6.77 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.54 (t, *J* = 7.3 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 2H), 5.55 (s, 1H), 4.12 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.72 (s, 3H), 3.69 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.22 (d, *J* = 14.3 Hz, 1H), 2.86 (d, *J* = 14.3 Hz, 1H), 2.81 (dq, *J* = 10.7, 7.0 Hz, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.78, 174.53, 159.86, 144.37, 142.17, 129.55, 128.27, 119.37, 116.97, 115.24, 113.13, 112.75, 64.37, 62.40, 59.96, 55.36, 43.71, 41.06, 29.59, 22.39, 14.02, 13.79.

IR (ATR): 3411, 2994, 1719, 1602, 1505, 1261, 1143, 738, 691 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(2-methoxyphenyl)pentanedioate (25)



Following the general procedure above, ethyl 2-(2-methoxyphenyl)acrylate (78.3 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (53.2 mg, 64%).

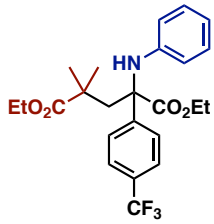
R_f = 0.23 (10% ethyl acetate in hexanes)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 6.96 (td, *J* = 7.6, 1.2 Hz, 1H), 6.92 – 6.83 (m, 2H), 6.65 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.52 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.42 – 6.34 (m, 2H), 5.38 (s, 1H), 4.19 – 4.02 (m, 2H), 3.88 – 3.75 (m, 1H), 3.55 (s, 3H), 3.28 – 3.15 (m, 2H), 2.61 (d, *J* = 14.2 Hz, 1H), 1.21 (s, 3H), 1.17 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.17, 173.74, 157.12, 145.61, 129.11, 128.75, 128.43, 127.87, 120.26, 117.46, 116.13, 111.38, 63.92, 61.67, 60.17, 55.35, 46.12, 40.98, 29.16, 24.00, 14.01, 13.99.

IR (ATR): 3368, 2975, 1734, 1598, 1265, 1135, 1023, 745, 688 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(4-(trifluoromethyl)phenyl)pentanedioate (26)



Following the general procedure above, ethyl 2-(4-(trifluoromethyl)phenyl)acrylate (41.1 mL, 0.2 mmol, 2.0 equiv), aniline (9.13 mL, 0.100 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (29.4 mL, 0.2 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (10% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (39.9 mg, 88%).

R_f = 0.21 (10% ethyl acetate in hexanes)

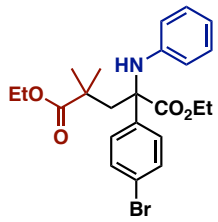
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 8.5, 6.8 Hz, 4H), 6.98 – 6.92 (m, 2H), 6.58 (t, *J* = 7.3 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 1H), 4.12 (qt, *J* = 7.1, 3.2 Hz, 2H), 3.70 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.20 (d, *J* = 14.2 Hz, 1H), 2.92 (d, *J* = 14.2 Hz, 1H), 2.84 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.56, 173.85, 144.61, 143.88, 129.83 (q, *J* = 32.5 Hz), 128.48, 127.48, 125.61 (q, *J* = 3.7 Hz), 124.11 (q, *J* = 272.0 Hz), 117.37, 115.20, 64.54, 62.69, 60.09, 43.95, 41.10, 29.37, 22.65, 13.99, 13.71.

^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.56 (s)

IR (ATR): 3396, 2981, 1726, 1603, 1506, 1323, 1070, 847, 747, 692 cm^{-1}

diethyl 2-(4-bromophenyl)-4,4-dimethyl-2-(phenylamino)pentanedioate (27)



Following the general procedure above, ethyl 2-(4-bromophenyl)acrylate (75.2 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in

hexanes). The product was obtained as a yellow oil, solidifies upon standing (60.2 mg, 65%).

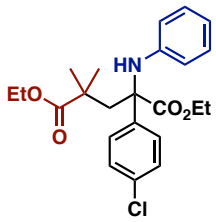
R_f = 0.34 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.99 – 6.92 (m, 2H), 6.57 (t, *J* = 7.3 Hz, 1H), 6.26 – 6.21 (m, 2H), 5.52 (s, 1H), 4.11 (qd, *J* = 7.2, 2.5 Hz, 2H), 3.69 (dq, *J* = 10.5, 7.0 Hz, 1H), 3.16 (d, *J* = 14.3 Hz, 1H), 2.85 (m, 2H), 1.27 (s, 3H), 1.20 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.63, 174.13, 144.01, 139.64, 131.81, 128.81, 128.43, 121.87, 117.24, 115.27, 64.26, 62.58, 60.06, 43.78, 41.08, 29.44, 22.55, 14.02, 13.78.

IR (ATR): 3391, 2978, 1721, 1601, 1506, 1267, 1140, 1008, 745, 720, 690 cm^{-1}

diethyl 2-(4-chlorophenyl)-4,4-dimethyl-2-(phenylamino)pentanedioate (28)



Following the general procedure above, ethyl 2-(4-chlorophenyl)acrylate (73.5 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in

hexanes). The product was obtained as a yellow oil, solidifies upon standing (53.1 mg, 64%).

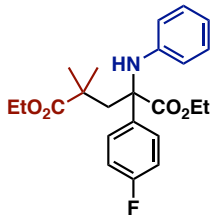
R_f = 0.34 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.98 – 6.92 (m, 2H), 6.57 (t, *J* = 7.3 Hz, 1H), 6.23 (d, *J* = 8.0 Hz, 2H), 5.51 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.69 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.16 (d, *J* = 14.3 Hz, 1H), 2.89 – 2.79 (m, 2H), 1.27 (s, 3H), 1.20 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.51, 174.08, 143.90, 138.94, 133.47, 128.72, 128.31, 128.28, 117.07, 115.13, 64.04, 62.42, 59.92, 43.68, 40.94, 29.31, 22.39, 13.87, 13.64.

IR (ATR): 3389, 2977, 1720, 1601, 1506, 1268, 1181, 1140, 1093, 1011, 840, 729, 690 cm^{-1}

diethyl 2,2-dimethyl-4-(phenylamino)-4-(4-fluorophenyl)pentanedioate (29)



Following the general procedure above, ethyl 2-(4-fluorophenyl)acrylate (70.4 mL, 0.4 mmol, 2.0 equiv), aniline (18.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®)

and purified by flash column chromatography (gradient, 5% to 15% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (61.1 mg, 76%).

R_f = 0.23 (10% ethyl acetate in hexanes)

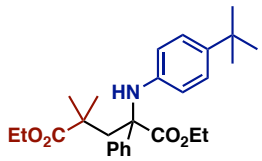
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.00 – 6.91 (m, 4H), 6.56 (t, *J* = 7.3 Hz, 1H), 6.24 (d, *J* = 8.0 Hz, 2H), 5.52 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.69 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.18 (d, *J* = 14.2 Hz, 1H), 2.91 – 2.79 (m, 2H), 1.28 (s, 3H), 1.20 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.55, 174.29, 162.04 (d, *J* = 247.0 Hz), 144.00, 136.03 (d, *J* = 3.4 Hz), 128.61 (d, *J* = 8.1 Hz), 128.23, 116.99, 115.42 (d, *J* = 21.6 Hz), 115.15, 63.94, 62.31, 59.89, 43.82, 40.95, 29.33, 22.35, 13.87, 13.63.

^{19}F NMR (471 MHz, Chloroform-*d*) δ -114.99 (tt, *J* = 9.4, 5.2 Hz)

IR (ATR): 3383, 2981, 1719, 1601, 1506, 1269, 1140, 744, 691 cm^{-1}

diethyl 2-((4-(*tert*-butyl)phenyl)amino)-4,4-dimethyl-2-phenylpentanedioate (30)



Data obtained in collaboration with Ms. Aja M. Nicely

Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), 4-*tert*-butylaniline (31.7 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-

methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 25% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (56.3 mg, 66%).

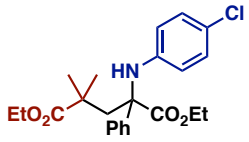
R_f = 0.34 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 – 7.43 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.20 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.17 (d, *J* = 8.5 Hz, 2H), 5.44 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.65 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.23 (d, *J* = 14.3 Hz, 1H), 2.90 (d, *J* = 14.3 Hz, 1H), 2.60 (dq, *J* = 10.5, 7.1 Hz, 1H), 1.28 (s, 4H), 1.21 (s, 3H), 1.19 (s, 9H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.73, 174.59, 141.67, 140.73, 139.24, 128.62, 127.47, 126.86, 125.01, 114.61, 64.32, 62.19, 59.79, 43.49, 40.98, 33.75, 31.59, 29.63, 22.29, 14.06, 13.71.

IR (ATR): 3401, 2466, 1723, 1267, 1141, 724 cm^{-1}

diethyl 2-((4-chlorophenyl)amino)-4,4-dimethyl-2-phenylpentanedioate (31)



Data obtained in collaboration with Ms. Aja M. Nicely

Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), 4-chlorolaniline (17.8 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 25% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (68.9 mg, 85%).

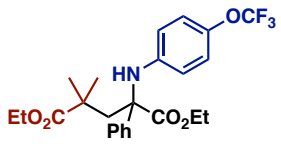
R_f = 0.29 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.25 – 7.19 (m, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.17 (d, *J* = 8.6 Hz, 2H), 5.62 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.73 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.18 (d, *J* = 14.3 Hz, 1H), 2.98 – 2.86 (m, 2H), 1.29 (s, 3H), 1.20 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.67, 174.40, 143.01, 139.91, 128.74, 128.10, 127.76, 126.77, 121.65, 116.30, 64.35, 62.45, 60.07, 43.51, 41.01, 29.61, 22.23, 13.96, 13.70.

IR (ATR): 3397, 2482, 1722, 1498, 1268, 1141, 726 cm^{-1}

diethyl 2-((4-trifuoromethoxyphenyl)amino)-4,4-dimethyl-2-phenylpentanedioate (32)



Data obtained in collaboration with Ms. Aja M. Nicely

Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), 4-trifluoromethoxyaniline (26.4 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 25% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (52.4 mg, 56%).

R_f = 0.29 (10% ethyl acetate in hexanes)

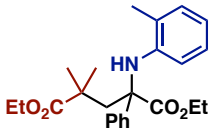
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.20 (d, *J* = 8.8 Hz, 2H), 5.67 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.70 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.20 (d, *J* = 14.3 Hz, 1H), 2.90 (d, *J* = 14.3 Hz, 1H), 2.77 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.65, 174.37, 143.18, 140.16 (q, *J* = 2.0 Hz), 139.87, 128.81, 127.84, 126.74, 121.43, 120.75 (q, *J* = 255.1 Hz), 115.35, 64.34, 62.49, 59.96, 43.39, 41.00, 29.74, 22.08, 13.85, 13.69.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -58.53.

IR (ATR): 3400, 2982, 1723, 1613, 1514, 1256, 1162, 1141, 1027, 725 cm^{-1}

diethyl 2-((2-methylphenyl)amino)-4,4-dimethyl-2-phenylpentanedioate (33)



Data obtained in collaboration with Ms. Aja M. Nicely

Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), 2-methylaniline (21.3 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 25% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (23.1 mg, 29%).

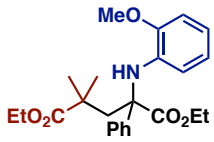
R_f = 0.39 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.17 (m, 3H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.69 – 6.62 (m, 1H), 6.46 (t, *J* = 7.3 Hz, 1H), 5.76 (d, *J* = 8.1 Hz, 1H), 5.54 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.58 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.24 (d, *J* = 14.3 Hz, 1H), 2.91 (d, *J* = 14.3 Hz, 1H), 2.66 (dq, *J* = 10.6, 7.1 Hz, 1H), 2.29 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.69, 174.97, 142.12, 140.48, 129.77, 128.67, 127.55, 126.72, 125.76, 122.96, 116.43, 113.77, 64.41, 62.36, 59.79, 43.14, 41.04, 29.61, 22.35, 17.87, 13.93, 13.74.

IR (ATR): 3401, 2981, 1722, 1607, 1516, 1271, 1142, 1028, 725 cm^{-1}

diethyl 2-((2-methoxyphenyl)amino)-4,4-dimethyl-2-phenylpentanedioate (34)



Data obtained in collaboration with Ms. Aja M. Nicely

Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), 2-methylaniline (22.4 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 25% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (28.9 mg, 35%).

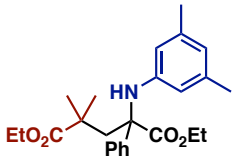
R_f = 0.26 (10% ethyl acetate in hexanes)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.7 Hz, 2H), 7.28 – 7.14 (m, 2H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.45 (dt, *J* = 22.7, 7.6 Hz, 2H), 6.19 (s, 1H), 5.79 (d, *J* = 7.8 Hz, 1H), 4.09 (q, *J* = 6.9 Hz, 2H), 3.89 (s, 3H), 3.71 – 3.58 (m, 1H), 3.17 (d, *J* = 14.3 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.90 (d, *J* = 14.4 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.65, 174.57, 147.49, 140.50, 134.35, 128.51, 127.45, 126.91, 120.14, 116.08, 114.03, 109.54, 64.40, 62.16, 59.90, 56.01, 43.79, 41.07, 29.19, 22.77, 13.91, 13.74.

IR (ATR): 3402, 2980, 1724, 1612, 1516, 1257, 1138, 1029, 728, 700 cm^{-1}

diethyl 2-((3,5-dimethylphenyl)amino)-4,4-dimethyl-2-phenylpentanedioate (35)



Data obtained in collaboration with Ms. Aja M. Nicely

Following the general procedure above, ethyl 2-phenylacrylate (67.7 mL, 0.4 mmol, 2.0 equiv), 2-methylaniline (25.0 mL, 0.200 mmol, 1.0 equiv), and ethyl-2-bromo-2-methylpropanoate (58.7 mL, 0.4 mmol, 2.0 equiv), were added to the reaction vial. After 24 hours, the crude mixture was then directly adsorbed onto diatomaceous earth (Celite®) and purified by flash column chromatography (gradient, 5% to 25% ethyl acetate in hexanes). The product was obtained as a yellow oil, solidifies upon standing (28.0 mg, 34%).

R_f = 0.37 (10% ethyl acetate in hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.40 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.18 (m, 1H), 6.19 (s, 1H), 5.87 (s, 2H), 5.43 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.73 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.21 (d, *J* = 14.2 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.05 (s, 6H), 1.29 (s, 3H), 1.21 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.88, 174.68, 144.31, 140.68, 137.47, 128.54, 127.40, 126.83, 118.85, 113.31, 64.40, 62.21, 59.98, 43.73, 41.05, 29.37, 22.59, 21.51, 13.87, 13.74.

IR (ATR): 3401, 2981, 1723, 1603, 1520, 1252, 1201, 1140, 726, 696 cm^{-1}

3.4 Product 17 crystallographic characterization.

Table 3.8. Crystal data and structure refinement for **17**.

Empirical formula	$C_{22}H_{27}NO_4$	
Formula weight	369.44	
Temperature	100.03(10) K	
Wavelength	1.54184 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.19400(10) Å	a= 94.7440(10)°.
	b = 17.9629(3) Å	b= 96.3820(10)°.
	c = 18.2730(3) Å	g = 96.3580(10)°.
Volume	1998.75(6) $Å^3$	
Z	4	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.677 mm^{-1}	
F(000)	792	
Crystal size	0.24 x 0.16 x 0.092 mm^3	
Theta range for data collection	2.444 to 73.474°.	
Index ranges	-7<=h<=7, -22<=k<=22, -20<=l<=22	
Reflections collected	38018	
Independent reflections	7933 [R(int) = 0.0245]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Gaussian and multi-scan	
Max. and min. transmission	1.00000 and 0.746	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7933 / 0 / 503	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0328, wR2 = 0.0799	
R indices (all data)	R1 = 0.0363, wR2 = 0.0825	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.278 and -0.202 $e.Å^{-3}$	

Figure 3.1. View of molecule 1 of **17** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

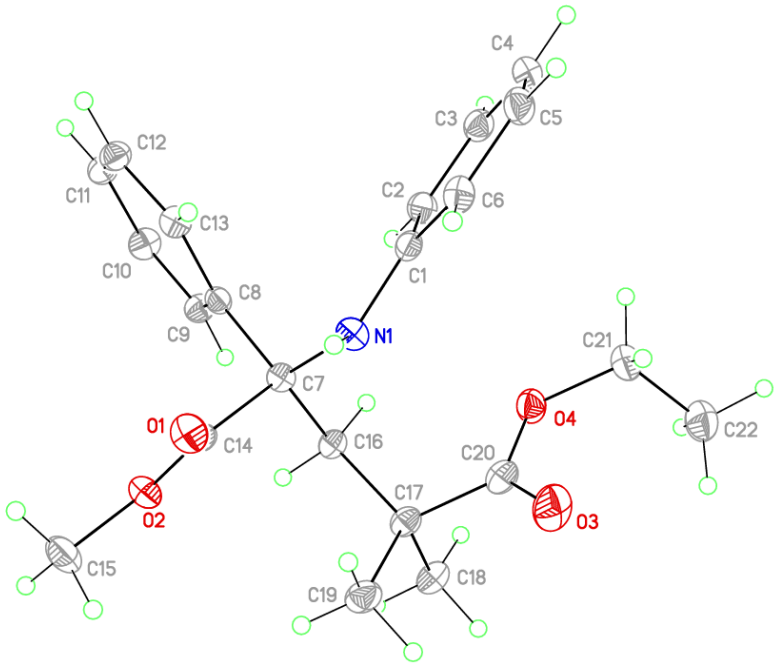
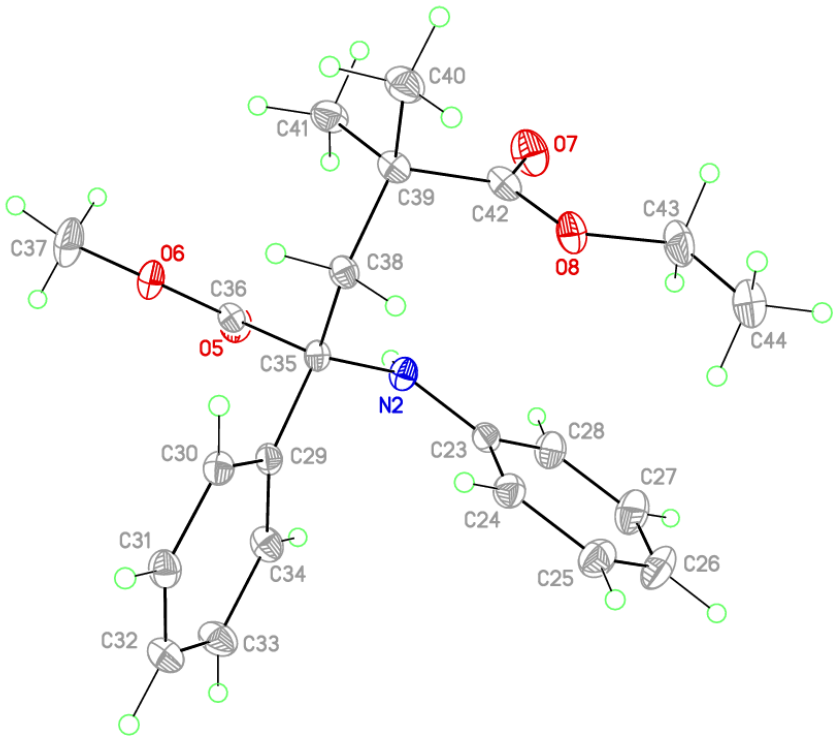


Figure 3.2. View of molecule 2 of **17** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.



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